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Perspective

PERSPECTIVE

COVID-19, a far cry from the influenza

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The outbreak of COVID-19 caused by SARS-CoV-2 was declared by the WHO to have reached the global pandemic level on 11 March 2020. As of 26 April 2020, more than 2 900 000 COVID-19 infection cases have been confirmed in more than 200 countries with at least 200 000 reported deaths.[1] Global reinforcement comprehensive interventions have been implemented to stop the pandemic. Unfortunately, since COVID-19 developed in December 2019, many people including the public and some professionals, have underestimated this destructive outbreak as a wave of influenza. Now that the nations have suffered great losses in lives, living, and the economy, it is time that such mistaken ideology be corrected and all people and countries treat COVID-19 seriously as a strongly contagious disease rather than the flu, if the humans wish to win this battle against the pandemic.

Why is COVID-19 often mistaken for influenza?

In many ways COVID-19 does look like the flu to laymen, and even physicians. Firstly, it broke out in the flu season, with similar main symptoms related to the respiratory tract. Both COVID-19 and influenza are characterized by typical chest CT presentation of ground-glass opacity and consolidation, and pathological features of diffuse alveolar damage (DAD). Moreover, more than 80% of COVID-19 cases are mild or even asymptomatic.[2] As we all know, other types of human coronavirus can also lead to influenza-like illness. All these may have given people a false impression that this emerging disease is just one new subtype of influenza caused by SARS-CoV-2.

Secondly, lack of comprehensive knowledge about the emerging COVID-19 has made it difficult to precisely assess its infectivity, particularly in the early stages. The extraordinarily stringent measures taken in China at the early stage of epidemic, including city lockdown, successfully controlled the infection and mortality, making it sound like influenza to some extent. For example, even at its peak stage in China, the daily increase of new cases confirmed by nucleic testing was at the most 4000–5000, still less than in the current data in some developed countries. The number of deaths was always very low with a mortality less than 0.5% in most provinces other than Hubei Province in China. Even in the worst-hit city, Wuhan, the capital of Hubei Province in China, the mortality of COVID-19 gradually increased from 2% early in February to 4% early in April, far less than that in Italy in early April. To those who regarded COVID-19 as just a wave of influenza, the later higher mortality in Hubei Province was explained as a result of the public health service being overwhelmed. The low mortality in China outside Hubei Province added to this misconception. However, such low mortality may be biased for the following reasons: 1) The other Chinese provinces adopted prompt and strict measures to contain the spread of COVID-19 in the very early stages, including denying entry for travelers from Hubei Province, not limited to Wuhan, and testing SARS-CoV-2 in suspected patients. Early diagnosis and treatment also substantially reduced the mortality. 2) Most patients were young adults with strong immunity, thus having lower mortality. 3) Because

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of the small number of patients identified outside Hubei Province, the medical resources were enough for their treatment. 4) The social distancing regulations including compulsory face mask wearing in public places contributed to effective control of the morbidity and mortality in provinces outside Hubei in China. In addition, in the countries that implemented very strict and effective measures, the infectivity and mortality are both very low (0.6% in South Korea[3] and zero reported for Singapore[4]), tending to mislead the public into an understanding that COVID-19 is nothing more serious than influenza.

How is COVID-19 different from influenza?

In terms of pathogenic mechanisms and pathological changes, SARS-CoV-2, the virus causing COVID-19, belongs to β coronaviruses, whose invading receptors are angiotensin-converting enzyme 2 (ACE2), the same as SARS-CoV and MERS-CoV. ACE2 is widely distributed in various human organs, which leads to DAD with cellular fibrinous exudates in COVID-19.[5] In contrast, influenza is an acute respiratory disease caused by influenza viruses, with the pathogenicity being based on the surface viral antigens, hemagglutinin (HA), and neuraminidase (NA), whose entry points are the sialic acid receptors on the host cell surface.[6] H1N1 can attach to both α-2,3-sialic acid (SA) in the lower respiratory tract and α-2,6-SA in the upper respiratory tract, so its pathological manifestations of the respiratory system include DAD, extensive hemorrhage, and necrotizing bronchiolitis of small airways, and necrosis, epithelial hyperplasia, and squamous metaplasia of large airways.[7] In contrast, H5N1 attaches only to α-2,3-SA, so it mainly attacks alveolae and bronchioles, and the dominating pathological findings in H5N1 are apoptosis of alveolar epithelial cells, DAD, and extensive hemorrhage in the lung.[8–11] It is worth noting that although DAD is the common manifestation in chest imaging for COVID-19, H1N1, and H5N1, COVID-19 is unique in the diffused bilateral ground-glass opacities,[12] while the typical presentations for H1N1 and H5N1 are consolidation in the disease area.[13,14] Despite similarities between the two diseases, their differences in pathogenic mechanism and pathological changes should help to differentiate COVID-19 from influenza.

In clinical manifestations, COVID-19 can cause systemic inflammation reaction and multiple organ dysfunction syndrome because its receptors are widely distributed in multiple human organs.[15] It involves not only the respiratory system but also the digestive, cardiovascular, and nervous systems, therefore symptoms often manifest in these systems.[16–19] Among them, there is a high incidence of gastrointestinal (GI) symptoms. In a retrospective study, 74 of 651 (11.4%) COVID-19 patients presented with GI symptoms at admission, including anorexia, nausea, or diarrhea.[20] According to a Chinese report, symptoms occurred in up to 79.1% COVID-19 patients.[21] Furthermore, GI symptoms are associated with the severity of COVID-19, with a higher incidence of diarrhea, nausea, or vomiting in severe cases,[22] and in patients admitted to the intensive care unit (ICU).[23] GI damage in COVID-19 infection has been proven by GI endoscopy and histological examination, besides viral nucleocapsid proteins detected in the damage sites.[24] Moreover, the detection of virus in stool provides liable evidence for the fecal-oral route of COVID-19.[24] The potential mechanisms of GI damage in COVID-19 could be attributed to the high expression of ACE2 in GI, particularly in the colon.[25]

In transmissibility and severity, the basic reproductive number (R0) of COVID-19 was estimated to be 2.2–3.79,[26,27] compared with R0 of 1.3–1.7 for the H1N1 outbreak in Mexico in 2009,[26] and that of 1.14 in H5N1,[28] indicating a much higher transmissibility of COVID-19 than influenza. Moreover, COVID-19 has a mean incubation period of 5.2 days, as compared to H1N1 (2 days) and H5N1 (5 days).[26,28] Notably, asymptomatic transmissions have been confirmed in COVID-19 patients, with a communicable period up to 3 weeks.[29] These data show that COVID-19 transmission is substantially stronger than influenza. As disease severity is concerned, COVID-19 has shown an unprecedentedly high fatality rate (7% for global and 13.5% for Italy up to 26 April 2020),[1] far greater than others, even the 1918 influenza (2%).[30] In addition, the reported rates of severe cases and the fatality rate of severe cases are 15.6% and 8.1% in COVID-19,[22] but 5% and 7%, respectively, in H1N1.[26] Considering the advances made in healthcare, the contrasts in these indices could further signify that COVID-19 is actually more devastating than influenza (Table 1).

Some lessons should be highlighted

When a new respiratory epidemic emerges, we should treat it with caution and should not take for granted that it is just another wave of influenza. It is very clear that it takes time for us to understand the disease as it spreads, and that incorrect preconceptions may hinder our attempts to curb outbreaks and save lives. It is imperative to be cautious about the potential pending epidemic of an emerging infectious disease and be prepared in terms of resources including personal protective equipment (PPE) and medical services to contain the potential outbreak in its early stages. Moreover, diagnostic technologies should be applied to any suspected cases as early as possible. Recently, Kang Zhang and colleagues found that artificial intelligence (AI) technologies could distinguish the chest CT of COVID-19, common pneumonia, and normal controls with very high accuracy, sensitivity, and specificity.[31] The applications of AI and other new information technologies could be integrated in early diagnostics and treatment for COVID-19. Setting up a series of protocols and guidelines for monitoring infectious diseases and tracing suspected infection is essential to recognize and isolate the suspected cases, then block disease transmission in the early stages.

Table 1. Similarities and differences between COVID-19 and influenza.

		COVID-19	Influenza
Similarities	Main symptoms	Respiratory symptoms and fever	
	Typical chest CT presentations	Ground-glass opacity and consolidation	
	Pathological feature	Diffuse alveolar damage	
Differences	Virus	β coronaviruses	Influenza viruses
	Invading receptors	Angiotensin-converting enzyme 2	Sialic acid receptors
	Route of transmissions	Various transmissions	Mainly by respiratory tract
	Clinical manifestations	Systemic disease	Mainly in the respiratory system
	Chest imaging feature	Ground-glass opacities	Consolidation
	Reproductive number	2.2–3.79	1.3–1.7 in H1N1 and 1.14 in H5N1
	Mean incubation period	5.2 days	2 days in H1N1 and 5 days in H5N1
	Mortality	4.9%–11.7%	2% in 1918 influenza and 1% in H1N1
	Severe cases	15.6%	5% in H1N1
	Fatality rate of severe disease	8.1%	7% in H1N1

More policies and sufficient funds also should be allocated for infectious disease research including its basic and translational medicine, and developing vaccines. The shortage in ventilators and other equipment in hospitals during the present pandemic reminds us that hospital facility planning should be further refined to meet the demands of severe cases, such as high use of ventilation and more intensive care resources. Furthermore, the current high incidence and mortality of COVID-19 in many countries also indicate the insufficiency of such organizations and institutions, including national health systems (NHS) and centers for disease control and prevention (CDC), in coping with emergencies. Thus, both NHS and CDC are warranted to be reinforced in the future. For COVID-19, given its high infectivity against a global background, all countries should stay together to fight against this pandemic.

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Conflicts of interest statement

None declared.

References

1. Worldometers. *COVID-19 Coronavirus Pandemic*, 2020; https://www.worldometers.info/coronavirus/#countries (accessed April 26, 2020).
2. Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus Disease 2019 (COVID-19) outbreak in China: Summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020;**323**:1239–42. doi:10.1001/jama.2020.2648.
3. Adams JG, Walls RM. Supporting the health care workforce during the COVID-19 global epidemic. *JAMA* 2020;**323**:1439–40. doi:10.1001/jama.2020.3972.
4. Young BE, Ong SWX, Kalimuddin S, *et al*. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. *JAMA* 2020;**323**:1488–94. doi:10.1001/jama.2020.3204.
5. Xu Z, Shi L, Wang Y, *et al*. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020;**8**:420–2. doi:10.1016/S2213-2600(20)30076-X.
6. Weis W, Brown JH, Cusack S, *et al*. Structure of the influenza virus haemagglutinin complexed with its receptor, sialic acid. *Nature* 1988;**333**:426–31. doi:10.1016/0042-6822(92)90541-v.
7. Mauad T, Hajjar LA, Callegari GD, *et al*. Lung pathology in fatal novel human influenza A (H1N1) infection. *Am J Respir Crit Care Med* 2010;**181**:72–9. doi: 10.1164/rccm.200909-1420OC.
8. Uiprasertkul M, Kitphati R, Puthavathana P, *et al*. Apoptosis and pathogenesis of avian influenza A (H5N1) virus in humans. *Emerg Infect Dis* 2007;**13**:708–12. doi: 10.3201/eid1305.060572.
9. To KF, Chan PK, Chan KF, *et al*. Pathology of fatal human infection associated with avian influenza A H5N1 virus. *J Med Virol* 2001;**63**:242–6. doi:10.1002/1096-9071(200103)63:3<242::aid-jmv1007>3.0.co;2-n.
10. Ng WF, To KF. Pathology of human H5N1 infection: new findings. *Lancet* 2007;**370**:1106–8. doi:10.1016/S0140-6736(07)61490-1.
11. Korteweg C, Gu J. Pathology, molecular biology, and pathogenesis of avian influenza A (H5N1) infection in humans. *Am J Pathol* 2008;**172**:1155–70. doi:10.2353/ajpath.2008.070791.
12. Shi H, Han X, Jiang N, *et al*. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China a descriptive study. *Lancet Infect Dis* 2020; **20**: 425–34. doi: 10.1016/S1473-3099(20)30086-4.
13. Marchiori E, Zanetti G, Fontes CA, *et al*. Influenza A (H1N1) virus-associated pneumonia: high-resolution computed tomography-pathologic correlation. *Eur J Radiol* 2010; **80**:500–4. doi: 10.1016/j.ejrad.2010.10.003.
14. Qureshi NR, Hien TT, Farrar J, *et al*. The radiologic manifestations of H5N1 avian influenza. *J Thorac Imaging* 2006; **21**:259–64. doi:10.1097/01.rti.0000213573.94032.53.

15. Zhou P, Yang XL, Wang XG, *et al*. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020;**579**:270–3. doi: 10.1038/s41586-020-2012-7.
16. Li JO, Lam DSC, Chen Y, *et al*. Novel Coronavirus disease 2019 (COVID-19): the importance of recognising possible early ocular manifestation and using protective eyewear. *Br J Ophthalmol* 2020;**104**: 297–8. doi: 10.1136/bjophthalmol-2020-315994.
17. Zheng YY, Ma YT. COVID-19 and the cardiovascular system. *Nat Rev Cardiol* 2020;**17**:259–60. doi:10.1038/s41569-020-0360-5.
18. Gu J, Han B, Wang J. COVID-19: gastrointestinal manifestations and potential fecal-oral transmission. *Gastroenterology* 2020;**158**:1518–9. doi:10.1053/j.gastro.2020.02.054.
19. Zhou L, Zhang M, Gao J, *et al*. Sars-Cov-2: underestimated damage to nervous system. *Travel Med Infect Dis* 2020, **S1477–8939**: 30110–1. doi: 10.1016/j.tmaid.2020.101642.
20. Jin X, Lian JS, Hu JH, *et al*. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut* 2020;**69**:1002–9. doi:10.1136/gutjnl-2020-320926.
21. Fang Dan MJ, Guan J, Wang M, *et al*. Manifestations of digestive system in hospitalized patients with novel coronavirus pneumonia in Wuhan, China: a single-center, descriptive study. *Chin J Dig* 2020;**40**:151–6. doi:10.3760/cma.j.issn.0254-1432.2020.0005.
22. Guan WJ, Ni ZY, Liang W-H, *et al*. Clinical characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020;**382**:1708–20. doi:10.1056/NEJMoa2002032.
23. Wang D, Hu B, Hu C, *et al*. Clinical characteristics of 138 hospitalized patients with 2019 Novel Coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020;**323**:1061–9. doi:10.1001/jama.2020.1585.
24. Xiao F, Tang M, Zheng X, *et al*. Evidence for gastrointestinal infection of SARS-CoV-2. *Gastroenterology* 2020;**158**:1831–3. doi:10.1053/j.gastro.2020.02.055.
25. Zhang H, Kang Z, Gong H, *et al*. The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes. *bioRxiv* 2020;**69**:1010–1018. doi:10.1101/2020.01.30.927806.
26. Tang X, Du R, Wang R, *et al*. Comparison of hospitalized patients with Acute Respiratory Distress Syndrome caused by COVID-19 and H1N1. *Chest* 2020;**S0012-3692**:30558–4. doi:10.1016/j.chest.2020.03.032.
27. Li C, Xu J, Liu J, *et al*. The within-host viral kinetics of SARS-CoV-2. *Math Biosci Eng* 2020;**17**:2853–2861. doi:10.1101/2020.02.29.965418.
28. Yang Y, Halloran ME, Sugimoto JD, *et al*. Detecting human-to-human transmission of avian influenza A (H5N1). *Emerg Infect Dis* 2007;**13**:1348–53. doi: 10.3201/eid1309.070111.
29. Hu Z, Song C, Xu C, *et al*. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. *Sci China Life Sci* 2020;**63**:706–11. doi:10.1007/s11427-020-1661-4.
30. Gates B. Responding to Covid-19 - A Once-in-a-Century Pandemic? *N Engl J Med* 2020;**382**:1677–9. doi:10.1056/NEJMp2003762.
31. Zhang K, Liu X, Shen J, *et al*. Clinically applicable AI system for accurate diagnosis, quantitative measurements and prognosis of COVID-19 pneumonia using computed tomography. *Cell* 2020;**S0092–8674**:30551–1. doi:10.1016/j.cell.2020.04.045.