Time Kinetics of Viral Clearance and Resolution of Symptoms in Novel Coronavirus Infection

To the Editor:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; previously called "2019-nCoV"; the virus that causes coronavirus disease [COVID-19]) has infected >1,773,000 patients and killed >111,650 people worldwide as of April 13, 2020 (1). It has been reported that a patient in Germany had high viral titers after the resolution of fever and infected two close contacts after the resolution of symptoms (2). In the wake of these cases, it is still unclear how long the patient was virus positive after the resolution of symptoms. In this study, we aimed to determine the time kinetics of viral clearance in reference to the resolution of symptoms in 16 patients treated in Beijing, China, and we show that half of the patients with COVID-19 were virus positive even after resolution of their symptoms.

Cases

We studied all 16 patients with confirmed COVID-19 released from the treatment center of People's Liberation Army General Hospital in Beijing, China, between January 28 and February 9, 2020. On alternate days, all patients had throat swabs collected, which were then analyzed. Patients were discharged after their recovery and confirmation of "virus-negative" status by at least two consecutive real-time PCRs (3). There was only one case of a false-negative result in our study: patient 6 had a negative test result followed by a positive detection and then two consecutive negative tests. Travel and possible exposure history were obtained from the patients and noted on their records. Epidemiologically, 10 patients visited Wuhan after the outbreak; 3 had exposure to a known infected patient; 2 came in contact with people from Wuhan; and 1 had no known exposure. The basic clinical characteristics are given in Table 1. The median age was 35.5 years (range, 3–68 yr), with 11 of 16 being male. The major symptoms in these patients were fever (14 of 16), cough (11 of 16), pharyngalgia (5 of 16), and dyspnea (2 of 16). The day of onset and resolution of these symptoms were noted. Details of symptoms are indicated in the online supplement.

Ground-glass opacities were observed by computed tomography of the chest in both sides of the lungs in six patients and only in the right lung in one patient. Concentrations of C-reactive protein and procalcitonin between the first sample obtained at the time of hospitalization and the last sample obtained before discharge were comparable (Table 1).

All the patients received various medical care to treat COVID-19. Fifteen patients were treated with IFN-α together with other antiviral drugs, including oseltamivir (1 of 16), lopinavir/ritonavir (11 of 16), acyclovir (1 of 16), moxifloxacin (5 of 16), methylprednisolone (2 of 16), γ-globulin (2 of 16), vancomycin (1 of 16), and meropenem (1 of 16), either alone or in combination. Only one patient required respiratory support involving mechanical ventilation.

The time kinetics of symptom onset, duration of symptoms, and viral clearance is described in Table 1. The viral detection test was performed upon clinical presentation and repeated every other day until the patient had a negative test result. The negative test result was confirmed again the next day. Upon confirmation of the negative test result, the patient was asked to quarantine at home for the next 2 weeks, with a follow-up visit to the hospital after 1 week to confirm virus-negative status. The incubation periods were estimated on the basis of the history of the patient's travel or potential exposure. Our data show an incubation period of 5 days (interquartile range, 1–6 d) among the patients (except for patient 12, who had no specific exposure). The mean duration of symptoms was estimated to be 8 days (interquartile range, 6.25–11.5). Most important, half (8 of 16) of the patients remained virus positive (a surrogate marker of shedding) even after the resolution of symptoms (median, 2.5 d; range, 1–8 d). Some of our patients had other comorbidities, which included diabetes (2 of 16) and tuberculosis (1 of 16), both of which did not affect the time course of the disease. Similarly, the clinical course for the 3-year-old boy did not significantly differ from that of the rest of the patients.

Discussion

The current COVID-19 pandemic is the third and most lethal outbreak of coronavirus in the 21st century (4), in which the number of infections and mortality have surpassed those of both Middle East respiratory syndrome and severe acute respiratory syndrome within a short period (1, 5). Although the infection appears to be milder, with the most lethality in the older male population with preexisting morbidities (3, 6), it is contagious. The ability to spread may arise from the ability of the virus to transmit from subclinical patients. Cases have been reported in which patients infected their close contacts even after "apparent recovery" from the infection (2). This warrants investigation of the "shedding window" after the clinical recovery of the patient. In this study, we report that half of the patients continued to be virus positive even after the resolution of symptoms up to 8 days (Figure 1). The viral clearance kinetics were similar in another study by Young and colleagues (12 d), in which all the patients survived the infection (7). In contrast, the virus persisted for 20 days in another study, which had a significant high mortality of >40% (8). This information can provide a useful tool for clinicians and policy makers to ensure that recovered patients do not spread the virus. It is important to note that all our patients had milder infections and recovered from the disease. However, it is currently unclear if there is a delayed viral clearance in the more vulnerable population, such as those who are older, have immunodeficiencies, or are receiving immunosuppressive therapies.

The current data are derived from mostly young and male subjects, which is consistent with our previous report in Beijing (9). Similarly to a recent study, we report the case of a child (3-yr-old boy) with COVID-19, indicating the ability of this virus to infect young children (10).

Our study is limited by the number of patients because there have been limited cases outside the epicenter of the coronavirus outbreak that have been successfully treated so far in which the patients were able to be released from the hospital. Our study provides initial insight into

Supported by funding from China 13th Five-Year National Key Grant (2018ZX09201013 [L.X.]), China Scholarship Council (201809112037 [D.C.]), Beijing Nova Program (Z171100001117012 [D.C.]), and Beijing Nova Program Interdisciplinary Cooperation Project (Z191100001119021 [D.C.]).

This letter has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Originally Published in Press as DOI: 10.1164/rccm.202003-0524LE on March 23, 2020

Table 1. Clinical Presentation and Two-Time Pertinent Laboratory Findings of Patient Population with COVID-19

	Median (IQR) (*n* = 16)*
Age, yr	35.5 (24–43)
Days from onset of symptoms to hospital admission	3.5 (3–4)
Days from onset of symptoms to positive viral test	3 (2–4)
Days from onset of symptoms to virus negativity	10.5 (6–12)
Days from onset of symptoms to resolution of symptoms	8 (6.25–11.5)
Days of hospitalization	6.5 (5.25–11)
Days from virus positivity to virus negativity	5.5 (4–8)
Days between virus negativity to resolution of symptoms (in 8 patients who continued to be virus positive after resolution of symptoms)	2.5 (1.25–4.5) (*n* = 8)
Incubation period	5 (1–6)
Fever, *n* (%)	14 (87.5%)
Febrile days	6.5 (5–8)
Cough, *n* (%)	11 (68.75%)
Productive cough, *n* (%)	3 (18.75%)
Pharyngalgia, *n* (%)	5 (31.25%)
Dyspnea, *n* (%)	2 (12.5%)
Diarrhea, *n* (%)	1 (6.25%)
Weakness, *n* (%)	5 (31.25%)
Dizzy, *n* (%)	2 (12.5%)

	Mean (SD) (*n* = 16)	
	During Admission	Before Discharge
WBCs, $\times 10^9$/L	5.484 (2.44)	6.331 (1.564)
Neutrophils, %	58.22 (16.30)	60.17 (14.45)
Absolute neutrophils, $\times 10^9$/L	3.35 (2.60)	3.879 (1.62)
Lymphocytes, %	32.47 (15.19)	29.61 (13.68)
Absolute lymphocytes, $\times 10^9$/L	1.633 (0.88)	1.807 (0.91)
Monocytes, %	7.689 (2.01)	7.359 (1.93)
Absolute monocytes, $\times 10^9$/L	0.4053 (0.14)	0.4513 (0.10)
Eosinophils, %	1.347 (1.15)	2.499 (2.35)
Absolute eosinophils, $\times 10^9$/L	0.08067 (0.09)	0.1693 (0.22)
Basophils, %	0.28 (0.22)	0.3853 (0.17)
Absolute basophils, $\times 10^9$/L	0.01533 (0.01)	0.024 (0.01)
RBCs, $\times 10^{12}$/L	4.498 (0.94)	4.718 (0.64)
Hb, g/L	130.4 (28.9)	136.5 (18.75)
Platelets, $\times 10^9$/L	162.6 (59.44)	233.5 (97.75)
CRP, mg/L	24.81 (41.18)	11.52 (22.67)
PCT, ng/ml	0.6821 (2.45)	0.1325 (0.36)
Fe, μmol/L	16.24 (6.96)	15.71 (7.29)
IL-6, pg/ml	18.14 (18.83)	11.66 (17.69)
Serum ferritin, ng/ml	341.4 (227.2)	402.4 (405.20)

Definition of abbreviations: COVID-19 = coronavirus disease; CRP = C-reactive protein; IQR = interquartile range; PCT = procalcitonin; RBCs = red blood cells; WBCs = white blood cells.
*Unless otherwise noted.

the viral clearance kinetics and the ability of the virus to persist even after the resolution for as long as 8 days, which may pose a significant challenge in controlling the spread of the disease. However, further studies are needed to investigate whether the real-time PCR–detected virus is capable of transmission at the later stage of the disease. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

De Chang, M.D., Ph.D.*
Guoxin Mo, M.D.*
Xin Yuan, M.D.*
Yi Tao, M.D.
Chinese People's Liberation Army General Hospital
Beijing, China

Xiaohua Peng, M.D.
Yale University School of Medicine
New Haven, Connecticut

Fu-Sheng Wang, M.D.‡
Lixin Xie, M.D.§
Chinese People's Liberation Army General Hospital
Beijing, China

Lokesh Sharma, Ph.D.‖
Charles S. Dela Cruz, M.D., Ph.D.‖
Yale University School of Medicine
New Haven, Connecticut

Enqiang Qin, M.D.‖
Chinese People's Liberation Army General Hospital
Beijing, China

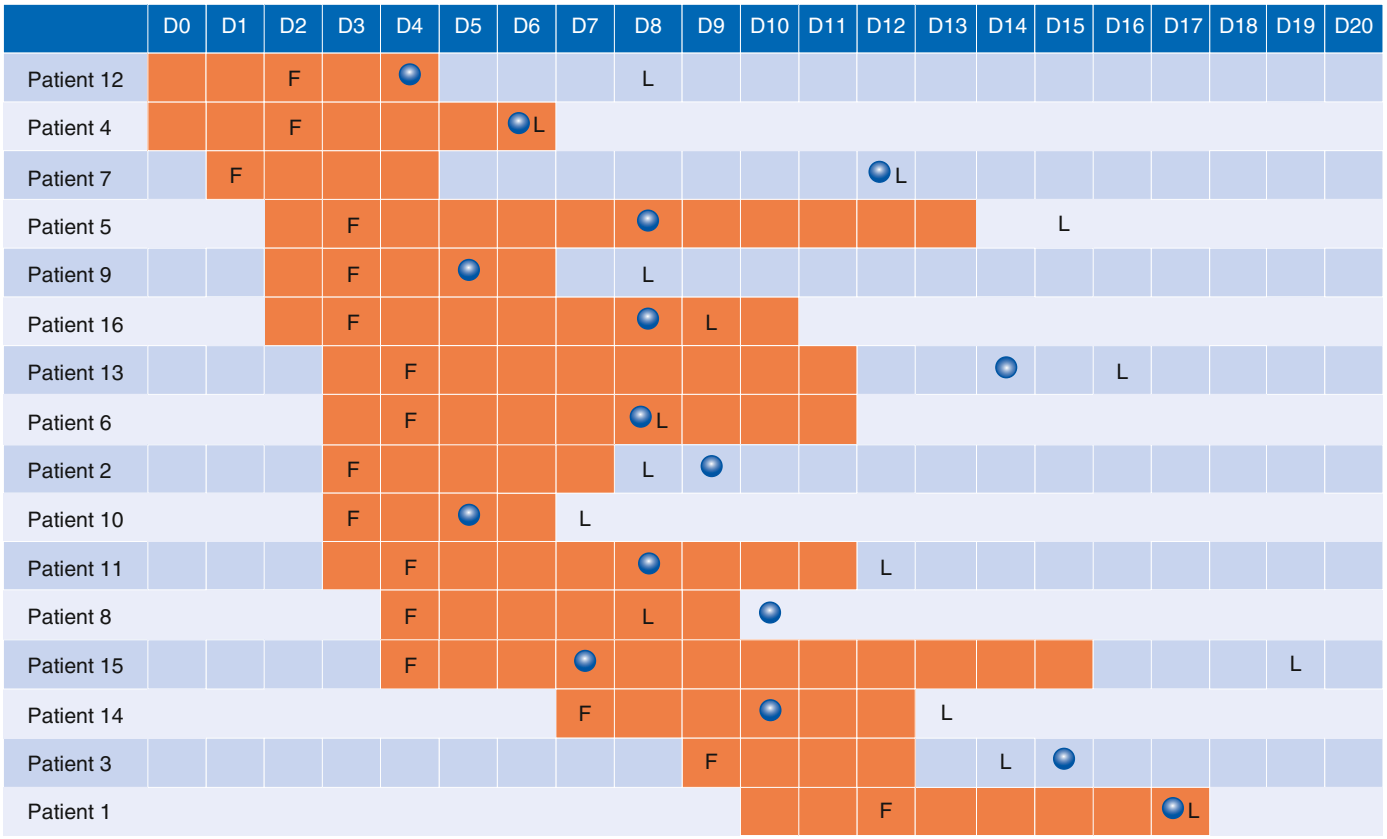

Figure 1. Time kinetics of viral presence in relationship with resolution of symptoms. Day 0 (D0) is the first day of symptoms, whereas the blue dots indicate the resolution of symptoms. The first orange box represents the day of first positive viral detection, and the last orange box indicates the day of first negative viral quantitative PCR. F = first time point at which laboratory blood tests were conducted during the hospitalization; L = last time point at which laboratory blood tests were conducted during the hospitalization.

*These authors contributed equally as first authors.
‡Corresponding author (e-mail: fswang302@163.com).
§Corresponding author (e-mail: 2464277169@qq.com).
||These authors contributed equally as senior authors.

References

1. World Health Organization (WHO). Coronavirus disease 2019 (COVID-19): situation report—84. Geneva: WHO; 13 April 2020.
2. Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, *et al*. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. *N Engl J Med* 2020;382:970–971.
3. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, *et al*. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med* 2020; 382:1199–1207.
4. Carlos WG, Dela Cruz CS, Cao B, Pasnick S, Jamil S. Novel Wuhan (2019-nCoV) coronavirus. *Am J Respir Crit Care Med* 2020;201: P7–P8.
5. Su S, Wong G, Shi W, Liu J, Lai ACK, Zhou J, *et al*. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. *Trends Microbiol* 2016;24:490–502.
6. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497–506. [Published erratum appears in *Lancet* 395:496.]
7. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, *et al*.; Singapore 2019 Novel Coronavirus Outbreak Research Team. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. *JAMA* [online ahead of print] 3 Mar 2020; DOI: 10.1001/jama.2020.3204.
8. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* [online ahead of print] 11 Mar 2020; DOI: 10.1016/S0140-6736(20)30566-3.
9. Chang D, Lin M, Wei L, Xie L, Zhu G, Dela Cruz CS, *et al*. Epidemiologic and clinical characteristics of novel coronavirus infections involving 13 patients outside Wuhan, China [letter]. *JAMA* 2020;323:1092–1093.
10. Wei M, Yuan J, Liu Y, Fu T, Yu X, Zhang ZJ. Novel coronavirus infection in hospitalized infants under 1 year of age in China [letter]. *JAMA* [online ahead of print] 14 Feb 2020; DOI: 10.1001/jama.2020.2131.

Lower Bacillus Calmette-Guérin Protection against *Mycobacterium tuberculosis* Infection after Exposure to Beijing Strains

To the Editor:

The *Mycobacterium tuberculosis* Beijing genotype family has been associated with large outbreaks of tuberculosis (TB), and comparisons of *M. tuberculosis* genotypes across populations has led to the suggestion that bacillus Calmette-Guérin (BCG) vaccination may select for Beijing genotype strains in a way that explains their global expansion (1). We used a case