The discussion says “Our results... suggest a decline in transmission in Wuhan in late January, 2020, around the time that control measures were introduced.” The daily number of new cases actually kept climbing for another 29 days after the city was sealed off. Considering that asymptomatic transmission was accounted for but the 5–2 days used as the crucial incubation period was too short—relative to a wide range of 0–24 days or an average of 6–4 days—was this discrepancy attributable to underestimation of the incubation period?

We believe that the modelling would be more instructive if it considered comparisons between absence of, presence of, or delays in lockdown. Such data would benefit timely policy making.

We declare no competing interests.

Nian Xiong, Tao Wang, *Zhicheng Lin
nianxiong@hust.edu.cn

Medical Treatment Expert Group for COVID-19 and Wuhan Red Cross Hospital, Wuhan, China (NX); Department of Neurology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China (NX, TW); Harvard Medical School, Belmont, MA, USA (ZL)

1 Kucharski AJ, Russell TW, Diamond C, et al. Early dynamics of transmission and control of COVID-19: a mathematical modelling study. Lancet Infect Dis 2020; published online March 11. https://doi.org/10.1016/S1473-3099(20)30144-4

2 Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med 2020; 382: 1199–207.

3 Huang LL, Shen SP, Yu P, Wei YY. [Dynamic basic reproduction number based evaluation for current prevention and control of COVID-19 outbreak in China]. Zhonghua Liu Xing Bing Xue Za Zhi 2020; 41: 466–69 (in Chinese).

4 Wang Y, Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicated special control measures. J Med Virol 2020; published online March 5. DOI:10.1002/jmv.25748

Authors’ reply

We thank Nian Xiong and colleagues for their response to our Article.1 Although we separated individuals into exposed and infectious compartments in the basic model, we also considered a sensitivity analysis whereby people became infectious in the second half of their incubation period, and obtained the same conclusion (Article appendix p 12). We allowed the reproduction number, R, to vary over time in our model, rather than simply fix this value, to capture possible variation in transmission as a result of control measures and behaviour change. However, our median estimate for the reproduction number in mid-January of 2.4 is consistent with other estimates from the same period by use of a fixed R.2 As there is a delay from infection to symptom onset to hospitalisation, our model incorporated a delay to account for the time it takes for changes in transmission to be reflected in the observed data. Our estimate for transmission reduction was similar to that in another study, which focused on case counts in Wuhan and estimated that R had declined to around 1.3 by the last week of January, 2020.1 We disagree that our assumed incubation period was inappropriate; our assumption of a 5–2 day (SD 3.7) value is consistent with later studies that have estimated a similar value.4

Xiong and colleagues raise an important point about the need to disentangle the precise drivers of the reduction in transmission. Although our model estimated an overall reduction in transmission, we did not have sufficient data to identify precisely how social distancing, quarantine, travel restrictions, and other lifestyle changes influenced these dynamics. There is no clear evidence that variation in the viral genome has driven changes in transmission,5 but sequence data could be useful for understanding the expansion and size of the outbreak. In a follow-up study, we have considered the effect of the timing and length of a lockdown, and the implications for ongoing transmission.6 As more data become available on the timing of control measures and subsequent outbreak dynamics, we agree that it will be crucial to evaluate the effectiveness of measures to provide a robust evidence base for future policymaking.

We declare no competing interests.

*Adam J Kucharski, Rosalind M Eggo
adam.kucharski@lshtm.ac.uk

Centre for Mathematical Modelling of Infectious Diseases, London School of Hygiene & Tropical Medicine, London, UK

1 Kucharski AJ, Russell TW, Diamond C, et al. Early dynamics of transmission and control of COVID-19: a mathematical modelling study. Lancet Infect Dis 2020; published online March 11. https://doi.org/10.1016/S1473-3099(20)30144-4

2 Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med 2020; 382: 1199–207.

3 Lauer SA, Grantz KH, Bi Q, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Intern Med 2020; published online March 10. DOI:10.7326/M20-0504.

4 Wang C, Liu L, Hao X, et al. Evolving epidemiology and impact of non-pharmaceutical interventions on the outbreak of coronavirus disease 2019 (COVID-19) in Wuhan, China. medRxiv 2020; published online March 6. DOI:10.1101/2020.03.03.20030593 (preprint).

5 MacLean DA, Ortiz R, Singer JB, et al. Response to “On the origin and continuing evolution of SARS-CoV-2”. 2020. http://virological.org/t/response-to-on-the-origin-and-continuing-evolution-of-sars-cov-2/418 (accessed March 27, 2020).

6 Prem K, Liu Y, Russell TW, et al. The effect of control strategies to reduce social mixing on outcomes of the COVID-19 epidemic in Wuhan, China: a modelling study. Lancet Public Health 2020; published online March 25. https://doi.org/10.1016/S2468-2667(20)30073-6.

Baricitinib for COVID-19: a suitable treatment?

As rheumatologists used to treating rheumatoid arthritis with Janus kinase (JAK) inhibitors and working in an area (Lombardy, Italy) with a high incidence of coronavirus disease 2019 (COVID-19), we read with great interest the Comment in The Lancet Infectious Diseases by Justin Stebbing and colleagues1 about the potential use of baricitinib for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The described mechanism affecting viral endocytosis mediated...
by two members of the numb-associated kinase family is one of the many unfamiliar effects of a relatively recent drug class, the real safety profile of which still remains to be definitively clarified. Undoubtedly, the fact that baricitinib can provide this antiviral effect at the approved dose for rheumatoid arthritis therapy is an undeniable advantage over other potential inhibitors of the same pathway.

However, some concern could arise from the best-known aspects of the mechanism of action of the drug and its safety profile. Interferon is one of the most powerful innate immune responses to prevent viral replication during the early phases of infection. Transcription through the JAK–STAT signalling pathway (mainly mediated by JAK1 and JAK2), activated by interferons, leads to the upregulation of many interferon-controlled genes that quickly kill viruses in infected cells. The importance of this defense mechanism is confirmed by the fact that most viruses have developed strategies to counteract the effects of interferons by blocking their signalling pathway, and viral-encoded factors that antagonise the JAK–STAT pathway are crucial determinants of virulence.7 As a consequence, JAK–STAT signal blocking by baricitinib (a selective JAK1 and JAK2 inhibitor) produces an impairment of interferon-mediated antiviral response, with a potential facilitating effect on the evolution of SARS-CoV-2 infection. This mechanism is thought to be involved in an increased risk of herpes zoster and simplex infection, which was reported in the development programme of baricitinib 4 mg compared with placebo (herpes zoster 4.2 per 100 person-years vs 1.0 per 100 person-years [p<0.05]; herpes simplex 5.4 per 100 person-years vs 2.2 per 100 person-years [p<0.05]).3

Notably, this complication also seems to be shared by the new JAK1 selective inhibitors upadacitinib and filgotinib.4 Viral infections (including herpes zoster and herpes simplex) in intensive care units can account for up to 10% of community-acquired and up to 5% of ventilator-associated pneumonia,5 the incidence of which might be expected to be higher in immunocompromised patients given JAK inhibitors.

In conclusion, we believe that, beyond the intriguing opportunity to directly block the penetration of SARS-CoV-2 into the cell, the use of baricitinib in susceptible patients with ongoing pneumonia associated with COVID-19 should be considered with extreme caution.

We declare no competing interests.

*Ennio G Favalli, Martina Biggioggero, Gabriella Maioli, Roberto Caporali
ennio.favalli@gmail.com

Division of Clinical Rheumatology, ASST Gaetano Pini-CTO Institute, Milan 20122, Italy (EGF, MB, GM, RC); and Department of Clinical Sciences and Community Health, Research Center for Adult and Pediatric Rheumatic Diseases, Università degli Studi di Milano, Milan, Italy (GM, RC)

1. Stebbing J, Phelean A, Griffin I, et al. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis 2020; 20: 400-02

2. Fleming SB. Viral inhibition of the IFN-induced JAK/STAT signalling pathway: development of live attenuated vaccines by mutation of viral-encoded IFN-antagonists. Vaccines (Basel) 2016; 4: 23

3. Smolen JS, Genovese MC, Takeuchi T, et al. Safety profile of baricitinib in patients with active rheumatoid arthritis with over 2 years median time in treatment. J Rheumatol 2019; 46: 7-18

4. Biggioggero M, Beccioli A, Crotti C, Agape F, Favalli EG. Upadacitinib and filgotinib: the role of JAK1 selective inhibition in the treatment of rheumatoid arthritis. Drugs Context 2019; 8: 212595

5. Kelesidis T, Mastors I, Metson A, Tsiodras S. How to approach and treat viral infections in ICU patients. BMC Infect Dis 2014; 14: 321

Authors’ reply

We thank Ennio Favalli and colleagues for their Correspondence regarding our suggestion to use baricitinib for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections.1 2 We also appreciate their recognition that inhibition of numb-associated kinase enzymes could indeed be beneficial in preventing virus infectivity via inhibition of clathrin-mediated endocytosis.

We welcome the opportunity to more fully explain the possible use of baricitinib in the current pandemic. Indeed, we accept that using a JAK1 and JAK2 inhibitor to treat a viral disease might appear illogical given that the antiviral effects of interferons are largely mediated by the JAK–STAT signalling pathway. However, the administration of pegylated-interferon has not had the beneficial antiviral effects originally hoped for,4 and clinical trials with interferons have yielded inconsistent results, with pathogenic effects of interferons being observed in some viral infections.

We speculate that in early asymptomatic disease and stages of the disease not requiring admittance to hospital, approximately 80% of patients with coronavirus disease 2019 (COVID-19) are able to clear the virus, largely through endogenous antiviral mechanisms, almost certainly including the interferons. Therefore, we do not recommend that baricitinib or other JAK inhibitors be given to these individuals. However, in patients with moderate disease requiring hospital care, the peak SARS-CoV-2 load occurs within approximately 7 days of symptom onset, and later, as the viral titre decreases in some patients, hyper-inflammation causes the severe phase of the disease,5 akin to a so-called cytokine storm. This clinically severe phase is accompanied by high levels of signalling, including increased levels of interferons α and β and IL-6, all of which signal through the JAK–STAT pathway. In a microarray study by Cameron and colleagues,6 the authors intriguingly showed that patients with severe acute respiratory syndrome (SARS) who had been discharged from hospital had low interferon α and interferon γ signalling activity, whereas in those with hypoxaemia who had died, interferon α and

Published Online
April 3, 2020
https://doi.org/10.1016/S1473-1099(20)30276-X