JMedSci

Journal of the Medical Sciences
(Berkala Ilmu Kedokteran)

Volume 52, Number 3 (SI), 2020; 125-133
http://dx.doi.org/10.19106/JMedSciSI005203202011

Convalescent plasma for COVID-19: a reasonable option for the pandemic based on both scientific and practical point of views

Mardiah Suci Hardianti[1*], Syahru Agung Setiawan[1], David Dwi Putera[2], Teguh Triyono[3], Jarir At Thobari[4], Johan Kurnianda[1]

[1]Division of Hematology-Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, [2]Siloam Hospitals Labuan Bajo, Nusa Tenggara Timur, [3]Department of Clinical Pathology and Laboratory Medicine, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, [4]Department of Pharmacology and Therapy, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

Submitted : 2020-04-29
Accepted : 2020-06-15

ABSTRACT

Convalescent plasma treatment has become a promising adjunctive option to treat COVID-19. Several case reports consistently supported the feasibility of this approach by showing the safety and improvements of clinical and laboratory aspects from the treated patients. However, more clinical trials are still required to establish the definitive statement about its potential effectiveness. We review the scientific basis for the application of convalescent plasma in COVID-19 to understand its potentials better. We also cover the potential risks and benefits for this treatment in order to be more selective and careful when preparing and deciding to apply this approach. Lastly, we summarize any important points to monitor after the administration of this treatment to prioritize safety and measure the effectiveness of the treatment.

ABSTRAK

Terapi plasma konvalesen atau plasma sembuh menjadi salah satu pilihan terapi pendukung yang menjanjikan pada kasus COVID-19. Beberapa laporan kasus yang ada sejauh ini mendukung kelayakan terapi ini dengan menunjukan keamanan dan perbaikan-perbaikan baik secara klinis maupun laboratoris. Meskipun demikian masih diperlukan uji klinis yang lebih besar dan desain studi yang lebih baik untuk sampai pada kesimpulan yang lebih meyakinkan mengenai efektivitas terapi ini. Kami merangkum dasar-dasar ilmiah penggunaan terapi plasma pada COVID-19 untuk memahami potensinya secara lebih baik. Selain itu kami juga menuliskan berbagai keuntungan dan juga berbagai risiko yang mungkin terjadi untuk membangun selektifitas dan kehati-hatian dalam penggunaannya. Di akhir, kami mencantumkan berbagai hal yang penting untuk dimonitor setelah pemberian terapi ini untuk tetap mengedepankan prinsip keamanan pada pasien disamping untuk mengukur kemanfaatan terapi.

Keywords:
convalescent plasma;
COVID-19;
treatment monitoring;
effectiveness;
safety;
clinical trial;

*corresponding author: mardiah.suci@ugm.ac.id

INTRODUCTION

Convalescent plasma (CP) is a plasma collected from a patient who has survived a previous infection and developed humoral immunity against the pathogen responsible for the disease. The transfusion of CP -a form of passive immunization- is expected to be able to neutralize the pathogen and eventually leads to its eradication from the blood circulation.[1] Thereof, it has been the subject of increasing attention, especially during an epidemic. The historical perspective of the use of convalescent plasma in viral infection back to the days of SARS CoV, H5N1 avian influenza, Ebola, Middle East Respiratory Syndrome (MERS) and H1N1 influenza epidemics.[2–6] In contrast with active vaccination that requires the induction of an immune response which takes time to develop and varies depending on the response of recipient, passive antibody administration provides immediate immunity to susceptible persons.[7] Our main objective to write this review was to share the scientific grounds of utilizing convalescent plasma (CP) in COVID-19.

Since there are two lines of immune system against viral infection i.e., innate or cellular immunity and adaptive or humoral immunity, the intriguing question regarding the use of convalescent plasma as passive adaptive or humoral immunity given to the patient would be: which is actually more important between innate and adaptive immunity in the eradication of SARS-CoV-2 infection? How necessary is the addition of passive adaptive immunity for clinical improvement in case of COVID-19?

The landscape of the immune responses in patients with COVID-19 is not yet completely clear. However, due to similar pathogenesis of SARS-CoV-2 with previous SARS-CoV infection, knowledge learned from SARS-CoV has essential points to understand the immune responses of this new coronavirus. This review will initially cover the scientific basis of CP in COVID-19 by referring to some articles explaining the immunopathogenesis of SARS-CoV infection, beside some newer review articles that proposed the immunopathogenesis of COVID-19. This part hopefully would give a defined basis to the following sub-topics which are more practical issues such as patient selection and consideration for timing of administration, donor selection and monitoring the effect of treatment to evaluate safety and effectiveness by referring to published works of utilizing CP in COVID-19.

DISCUSSION

Scientific basis of convalescent plasma in COVID-19

Basically, the use of convalescent plasma to overcome the infection is gained by the administration of antibodies contained in the plasma against a given agent from a recovered patient to an individual for the purpose of preventing or treating an infectious disease due to the agent. Effective innate immune response against viral infection relies heavily on the type Iinterferon (IFN) responses by the host upon a viral infection and its downstream cascade that culminates in controlling viral replication and induction of effective adaptive immune response.[8] Based on the accumulated data for previous coronavirus infection, innate immune response plays crucial role in protective or destructive responses. A successful mounting of type I IFN response should be able to suppress viral replication and dissemination at an early stage. However, with similar changes in increased total neutrophils and decrease in lymphocytes counts during COVID19, SARS-CoV-2 probably induces delayed type I IFN and loss of viral control in

an early phase of infection. Active viral replication later results in hyper-production of type I IFN and influx of neutrophils and macrophages which are the major sources of pro-inflammatory cytokines. The stimulation of these innate immune cells surrounding the lungs to create a cytokine storm by complement activation via direct, classical and alternative pathways are the main cause of acute respiratory distress syndrome (ARDS) in later stage of the disease.[9,10]

Adaptive immunity in the form of antibodies play their protective functions by several mechanisms : 1) antigen neutralization , mainly depends on interaction of the antigen-binding region (Fab) with antigen, 2) antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP), which require interactions between the constant region (Fc) of antibody with other proteins or immune effector cells. These Fc receptor-dependent antibody provides a direct link between the innate and adaptive immune systems, harnessing the potent anti-pathogen functions of the innate immune system, and overcoming its inherent limited pattern recognition capacity by utilizing the diversity and specificity of the adaptive immune response. Fc receptor-dependent antibody provides mechanisms for clearance of infected host cells, immune complexes, or opsonized pathogens, as well as activation of downstream adaptive immune responses by facilitating antigen presentation or by stimulating the secretion of inflammatory mediators.[11] These two mechanisms are generally included in the antibody-mediated opsonization. The complement-mediated opsonization via classical pathway which is another protective mechanism of the adaptive immune system might work as a double-edged weapon when it stimulates the innate cells,particularly neutrophils and macrophages, in the later stage of COVID19 to produce enormous amount of pro-inflammatory cytokine besides those cells infiltration at the site of organ dysfunction.[10]

SARS-CoV infection induces seroconversion as early as day 4 after onset of disease and was found in most patients by 14 days. Long lasting specific IgG and neutralizing antibody are reported as long as 2 years after infection.[12] A limited serology details of SARS-CoV-2 was reported where a patient showed peak specific IgM at day 9 after disease onset and the switching to IgG by week 2.[13]

Others resumed the two-phase of immune response induced by COVID-19 infection. First or early phase (immune defense-based protective phase) consists of the incubation and non-severe stage where a specific adaptive immune response is required to eliminate the virus and to preclude disease progression to severe stages. They recommend to boost the immune system during this stage to prevent the disease progression. Second or severe phase (inflammation-driven damaging phase) is where the inflammation feature becomes dominant causing the organs damage due to the impaired early immune response followed by the propagation of virus and cytokine storm.[14]

In case of SARS-CoV-2, the anticipated mechanism of action by which passive antibody therapy would mediate protection is by viral neutralization. However, the other aforementioned mechanisms via ADCC and ADCP may also be possible.[7]

Realizing the intertwine between innate and adaptive immune system, and how the adaptive immune system can back up and even harnessing the function of innate immunity, the utilization of convalescent plasma in COVID-19 patient is a very reasonable scientific option.

Patient selection and timing of administration for the use of convalescent plasma in COVID-19: balancing risks and benefits

A general principle of passive antibody therapy is that it is more effective when used for prophylaxis than for treatment of disease. When used for therapy, passive antibody is most effective when administered in earlier stage to enable the antibody neutralizing the viral antigen more effectively and modifying the inflammatory response easily than in later or established disease.[7]However, the reason to use it in the later stage of the disease is also based on several risks. The risks of passive administration of convalescent plasma fall into two categories, known and theoretical. The known risks are those associated with transfer of blood substances such as infection and any immunological reactions. Moreover when transfused to individuals with pulmonary disease plasma infusion carries some risk for transfusion related acute lung injury (TRALI).[7,15] The theoretical risk involves the phenomenon of antibody dependent enhancement of infection (ADE) wherein normal mechanisms of antigen-antibody complex clearance fail, and instead provide an alternate route for host cell infection.[16] For SARS and COVID-19, the protein sequences responsible for ADE have been identified on the spike (S) protein which is the main ligand of the SARS-CoV-2 for the entrance to the host cell via angiotensin converting enzyme-2 (ACE-2) receptor.[17]

Pre-existing anti-CoV IgG antibodies to common strains of CoV that infect humans, but also react with COVID-19 and induce ADE could be another risk factor for severe disease that partially explain its occurrence of in older adults.[18,19] In other words, the absence of high affinity anti-CoV IgG potentially explain the milder disease in children and younger adults.

Therefore, any efforts should be made to increase the potential benefit and decrease the risk such as cautious preparations from any potential harms particularly the preparation of high titers of neutralizing antibody that works selectively to neutralize SARS-CoV-2 antigens.[20,21]

Another theoretical risk is that antibody administration to those exposed to SARS-CoV-2 may prevent disease in a manner that attenuates the immune response, causing such individuals vulnerable to subsequent reinfection. This concern could be investigated as part of a clinical trial by measuring immune responses in those exposed and treated individuals with convalescent sera to prevent disease. If the risk proved real, these individuals could be vaccinated against COVID-19 when a vaccine becomes available.[7]

To date only limited clinical trials available (6 case reports, by April 20th 2020,) and all reports applied this approach as an adjunctive treatment particularly for severe and critically ill COVID-19 patient.[20–25] From these publications including 27 patients (1 mild aymptomatic, 1 moderately ill, 16 severe and 9 critical ill) there was only one mild immunological reaction in form of facial red spot, not a life-threatening condition.[21] The approval from FDA are also still limited convalescent plasma for severe and critically ill COVID-19.[26]

Beside any scientific considerations, this selection may be based on the facts that there is not yet any specific treatment for this disease. Allowing the immune defense-based protective phase to work optimally during the initial stage could be one of the safest way, although it does not prevent any further trial to apply this treatment for earlier stage or even possibly be a prophylaxis.[7,27]

Donor selection

Convalescent plasma is drawn from individuals who have recovered from COVID-19 who can donate blood, have had no symptoms for 14 days, and have had negative results on covid-19 tests.[26] General eligibility criteria for blood donation and vigilant procedures for screening any potential infections and transfusion reactions should be done. More important, the sufficiently high amount of antibody IgG titer by ELISA as well as appropriate anti-SARS-CoV-2 neutralizing antibody titer should be verified before the donation.[20,21,27] Some studies showed that ELISA IgG correlates well with neutralization titers in MERS cases so that it might be a sufficient screening test for plasma donation.[17,28] Four among six case reports that applied CP in COVID-19 did not mention any measurement of neutralizing antibody titers, including one case report from Korea that presumed its high titer due to history of severe clinical condition of the donors.[22–25] After the qualification of the donor, plasma collection can be done. Plasmapharesis is a preferred collection method. The most important reason for this method is the possible larger collected volume and less impact on the donor's haemoglobin level. A repetition of donation with 2 weeks intervals is also possible with plasmapharesis.[27] A blood donation followed by plasma fractionation is another method to obtain convalescent plasma that may become an option when plasmapharesis equipment is not available.

Monitoring the effect of treatment: safety and effectiveness

Safety and effectiveness are two important points to assess in the patient after the administration of convalescent plasma product. Close monitoring should be maintained during and after transfusion to detect any transfusion-related immediate adverse effects such as transfusion-associated circulation overload (TACO) and to detect any further unintended side effects which usually be related to any immunological reactions, particulary transfusion related acute lung injury (TRALI) or any systemic complications.[27]

The effectiveness of convalescent plasma treatment can be assessed from four aspects, as follow :

1) Clinical recovery response. From a variety of case series or clinical trials with limited subjects investigating the effect of convalescent plasma to COVID-19 patients, clinical parameters occupy top priority in assessing effectiveness, including resolution of symptoms such as dyspnea due to renormalization of blood oxygen saturation (SaO_2), changes in vital signs such as body temperature which turns into normal, or other important clinical outcomes such as extubation in previous ARDS patients, discharge from hospital, or patients with fatal conditions that die later.[20–22,25] Convalescent plasma obtained from recovered COVID-19 patients are considered to have humoral immunity, which is later perceived to have high levels of neutralizing antibodies that are sufficiently capable and could contribute to the viral clearance and symptom improvement.[20,21] In addition, evidenced from in vivo study of HIV-1 virus, it was reported that neutralizing antibodies could also increase the clearance of infected cells which also provide to alleviation of symptoms.[29]

2) Measurement of the antibody titers. In line with the previous point, it is known that virus-specific IgM and IgG antibody titers, including neutralizing antibody levels, are considered as the eligibility criteria of plasma donor candidate with variable cut-off titer between studies.[20,21,25,27] This shows that antibody parameters, including neutralization antibodies, are one of the most important therapeutic mechanisms

of convalescent plasma. It is known from previous reports, that patients who recovered from SARS-CoV infection will experience a slow but persistent increase in neutralizing antibody titers which is not observed in dead cases.[30] In conjunction with standard therapy, neutralizing antibodies in convalescent plasma will accelerate virus clearance and prevent the viral entry into the target cells.[31] Convalescent plasma transfusion is expected to contribute in increasing polyclonal antibody and neutralizing antibodies titers in COVID-19 patients which result on virus neutralization and lead to symptom improvement. Consequently, serial measurement of antibody titers in terms of IgM, IgG, and neutralizing antibodies titersarehighly recommended to monitor the therapeutic effectiveness.[20]

3) Resolution of acute inflammatory parameters. As with other infectious diseases, SARS-CoV-2 infection will cause an influx of neutrophils and monocytes/ macrophages which results in hyper-production of pro-inflammatory cytokine.[9] Most COVID-19 cases will be followed by an increase in neutrophils, decreased of lymphocytes, increased of IL-6 and CRP level, with in severe patients followed by elevation of Procalcitonin.[32,33] These parameters generally reflect acute yet severe inflammation occurred within SARS-CoV-2 infection. Based on previous studies, administration of standard therapy in conjunction with convalescent plasma was followed by decrease in pro-inflammatory parameters such as IL-6, CRP, and pro-calcitonin level, in addition to re-normalization of lymphocytes counts.[20–22] Contribution of neutralizing antibodies within convalescent plasma along with gaining function of patient's adaptive humoral immunity to undergo self-production of antibodies further helps accelerate viral clearance and ultimately reduce acute inflammatory effects of SARS-CoV-2 infection. Therefore, measurement of acute inflammatory parameters reflected by differential counts, CRP, pro-calcitonin and IL-6 is recommended to be a part of evaluation of convalescent plasma transfusion.

4) Resolution of the imaging result. Along with the improvement of pneumonia in COVID-19 patients clinically, it will also be followed by resolution of lung imaging. It was previously known that ground-glass opacities (GGO) and lung consolidation are the predominant findings in majority of COVID-19 cases with pneumonia.[34] Despite lower sensitivity compared with CT scans to detect abnormalities in COVID-19, chest X-ray is still being considered as first choice of imaging modality to triage the suspected cases in some countries, including Indonesia, due to limitation of CT facilities but relatively more affordable portable X-Ray with less risk of contamination.[35] Some studies reported improvement in terms of lung imaging within a week after transfusion of convalescent plasma, although they used serial CT scan.[21,23] Considering the similarity of findings between CT scans and chest X-rays in majority of COVID-19 cases with pneumonia, it is still possible to see these improvements with serial chest X-Ray which has also been reported by a case series in South Korea.[22] Therefore, radiological improvement could bring additional evidence of convalescent plasma effectiveness accompanied by monitoring of clinical status and laboratory parameters.

CONCLUSION

Convalescent plasma as adjunctive treatment for COVID-19 has a strong scientific basis to be utilized. Awareness of its potential risks and benefit help to determine the strategies to improve the treatment outcome and minimize the adverse events. Safety and effectiveness are two important points to assess in the patient following the treatment to

study the benefit and risk better and to define the effectiveness of treatment. Last but not least, despite still limited in the number of reports, the data consistently showed encouraging comprehensive result from the patients. More expanded clinical trials with more patients in number and better study designs are required to draw a more definitive statement about its potential effectiveness.

ACKNOWLEDGEMENT

The authors would like to thank Detty Siti Nurdiati, MD, MPH, Ph.D for great advice and invaluable scientific inputs of the manuscript.

REFERENCES

1. Marano G, Vaglio S, Pupella S, Facco G, Catalano L, Liumbruno GM, *et al.* Convalescent plasma: new evidence for an old therapeutic tool? Blood Transfus. 2016; 14(2):152–157. https://doi.org/10.2450/2015.0131-15
2. Zhou B, Zhong N, Guan Y. Treatment with convalescent plasma for influenza A (H5N1) iInfection. N Engl J Med 2007; 357(14):1450–1. https://doi.org/10.1056/NEJMc070359
3. Hung IFN, To KKW, Lee C-K, Lee K-L, Chan K, Yan W-W, *et al.* Convalescent plasma treatment rReduced mMortality in pPatients wWith sSevere pPandemic iInfluenza A (H1N1) 2009 vVirus iInfection. Clin Infect Dis 2011; 52(4):447–56. https://doi.org/10.1093/cid/ciq106
4. Florescu DF, Kalil AC, Hewlett AL, Schuh AJ, Stroher U, Uyeki TM, *et al.* Administration of brincidofovir and convalescent plasma in a patient with ebola virus disease. Clin Infect Dis 2015; 61(6):969–73. https://doi.org/10.1093/cid/civ395
5. Kraft CS, Hewlett AL, Koepsell S, Winkler AM, Kratochvil CJ, Larson L, *et al.* The use of TKM-100802 and convalescent plasma in 2 patients with Eebola virus disease in the United States. Clin Infect Dis 2015; 61(4):496–502. https://doi.org/10.1093/cid/civ334
6. van Griensven J, Edwards T, de Lamballerie X, Semple MG, Gallian P, Baize S, *et al.* Evaluation of cConvalescent pPlasma for Ebola vVirus dDisease in Guinea. N Engl J Med 2016; 374(1):33–42. https://doi.org/10.1056/NEJMoa1511812
7. Casadevall A, Pirofski L. The convalescent sera option for containing COVID-19. J Clin Invest 2020; 130(4):1545–8. https://doi.org/10.1172/JCI138003
8. Murira A &, Lamarre A. Type-i interferon responses: from friend to foe in the battle against chronic viral infection. Front Immunol 2016; 19:7. https://doi.org/10.3389/fimmu.2016.00609
9. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pacific J Aallergy Immunol 2020; 38(1):1–9. https://doi.org/10.12932/AP-200220-0772
10. Risitano AM, Mastellos DC, Huber-Lang M, Yancopoulou D, Garlanda C, Ciceri F, *et al.* Complement as a target in COVID-19? Nat Rev Immunol 2020; https://doi.org/10.1038/s41577-020-0320-7
11. Tay MZ, Wiehe K, Pollara J. Antibody-dependent cellular phagocytosis in antiviral immune responses. Front Immunol 2019; 28:10. https://doi.org/10.3389/fimmu.2019.00332
12. Liu W, Fontanet A, Zhang P, Zhan L, Xin Z, Baril L, *et al.* Two year prospective study of the humoral immune response of patients with severe acute respiratory syndrome. J Infect Dis 2006; 193(6):792–5. https://doi.org/10.1086/500469
13. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, *et al.* A pneumonia outbreak associated with a new coronavirus of probable bat origin.

Nature 2020; 579(7798):270–3. http://doi.org/10.1038/s41586-020-2012-7
14. Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, *et al.* COVID-19 infection: the perspectives on immune responses. Cell Death Differ 2020; 27(5):1451–4. https://doi.org/10.1038/s41418-020-0530-3
15. Gajic O, Rana R, Winters JL, Yilmaz M, Mendez JL, Rickman OB, *et al.* Transfusion-related acute lung injury in the critically Ill. Am J Respir Crit Care Med 2007; 176(9):886–91. https://doi.org/10.1164/rccm.200702-271OC
16. Tetro JA. Is COVID-19 receiving ADE from other coronaviruses? Microbes Infect 2020; 22(2):72–3. https://doi.org/10.1016/j.micinf.2020.02.006
17. Ko J-H, Seok H, Cho SY, Eun Ha Y, Baek JY, Kim SH, *et al.* Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single centre experience. Antivir Ther 2018; 23(7):617–22. https://doi.org/10.3851/IMP3243
18. Luke TC, Kilbane EM, Jackson JL, Hoffman SL. Meta-Analysis: convalescent blood products for Sspanish influenza pneumonia: a future Hh5Nn1 treatment? Ann Intern Med 2006; 145(8):599. https://doi.org/10.7326/0003-4819-145-8-200610170-00139
19. Wan Y, Shang J, Sun S, Tai W, Chen J, Geng Q, *et al.* Molecular mechanism for antibody-dependent enhancement of coronavirus entry. Gallagher T, editor. J Virol 2019; 94(5):e02015-19. https://doi.org/10.1128/JVI.02015-19
20. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, *et al.* Treatment of 5 critically ill patients with COVIDcovid-19 with convalescent plasma. JAMA 2020; 323(16):1582-9. https://doi.org/10.1001/jama.2020.4783
21. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, *et al.* Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci 2020; 202004168. https://doi.org/10.1073/pnas.2004168117
22. Ahn JY, Sohn Y, Lee SH, Cho Y, Hyun JH, Baek YJ, *et al.* Use of convalescent plasma therapy in two COVIDcovid-19 patients with acute respiratory distress syndrome in Korea. J Korean Med Sci 2020; 35(14):e149. https://doi.org/10.3346/jkms.2020.35.e149
23. Ye M, Fu D, Ren Y, Wang F, Wang D, Zhang F, *et al.* Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. J Med Virol 2020 Apr 15. https://doi.org/10.1002/jmv.25882
24. Zhang B, Liu S, Tan T, Huang W, Dong Y, Chen L, *et al.* Treatment with convalescent plasma for critically IiIIll patients with severe acute respiratory syndrome coronavirus-2 SARS-COV-2 infection. Chest 2020; S0012-3692(20)30571-7. https://doi.org/10.1016/j.chest.2020.03.039
25. Pei S, Yuan X, Zhang ZZ, Yao RR, Xie Y, Shen MM, *et al.* Convalescent p Plasma to t Treat COVID-19: Chinese Strategy and Experiences. Med Rxiv 2020; https://doi.org/10.1101/2020.04.07.20056440
26. Tanne JH. Covid-19: FDA approves use of convalescent plasma to treat critically ill patients. BMJ 2020; m1256. https://doi.org/10.1136/bmj.m1256
27. Tiberghien P, de Lambalerie X, Morel P, Gallian P, Lacombe K, Yazdanpanah Y. Collecting and evaluating convalescent plasma for COVID-19 treatment: why and how. Vox Sang. 2020. https://doi.org/10.1111/vox.12926
28. Choe PG, Perera RAPM, Park WB, Song K-H, Bang JH, Kim ES, *et al.* MERS-CoV Antibody rResponses 1 yYear after sSymptom oOnset, South Korea, 2015. Emerg Infect Dis 2017; 23(7):1079–84.

https://doi.org/10.3201/eid2307.170310
29. Lu C-L, Murakowski DK, Bournazos S, Schoofs T, Sarkar D, Halper-Stromberg A, *et al.* Enhanced clearance of HIV-1-infected cells by broadly neutralizing antibodies against HIV-1 in vivo. Science (80-) 2016; 352(6288):1001–4. https://doi.org/10.1126/science.aaf1279
30. Zhang L, Zhang F, Yu W, He T, Yu J, Yi CE, *et al.* Antibody responses against SARS coronavirus are correlated with disease outcome of infected individuals. J Med Virol 2006; 78(1):1–8. https://doi.org/10.1002/jmv.20499
31. Shen C, Chen J, Li R, Zhang M, Wang G, Stegalkina S, *et al.* A multimechanistic antibody targeting the receptor binding site potently cross-protects against influenza B viruses. Sci Transl Med 2017; 9(412):eaam5752. https://doi.org/10.1126/scitranslmed.aam5752
32. 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 2020; 395(10229):1054–62. https://doi.org/10.1016/S0140-6736(20)30566-3
33. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, *et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395(10223):507–13. https://doi.org/10.1016/S0140-6736(20)30211-7
34. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, *et al.* Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis 2020; 20(4):425–34. https://doi.org/10.1016/S1473-3099(20)30086-4
35. Wong HYF, Lam HYS, Fong AH-T, Leung ST, Chin TW-Y, Lo CSY, *et al.* Frequency and distribution of chest radiographic findings in COVID-19 positive patients. Radiology. 2019; 27:201160. https://doi.org/10.1148/radiol.2020201160