SCIENCE CHINA
Life Sciences

•LETTER TO THE EDITOR•

December 2022 Vol.65 No.12: 2556–2559
https://doi.org/10.1007/s11427-021-2115-7

Impact of inactivated COVID-19 vaccines on viral shedding in B.1.617.2 (Delta) variant-infected patients

Zhiliang Hu[1,2†], Yi Yin[3†], Kai Wang[4†], Miaomiao Xu[1], Chengyuan Ding[2], Yan Song[1], Changhua Yi[1], Junwei Li[1], Yongxiang Yi[1*] & Zhihang Peng[3*]

[1]*Nanjing Infectious Disease Center, the Second Hospital of Nanjing, Nanjing University of Chinese Medicine, Nanjing 210003 China;*
[2]*Center for Global Health, School of Public Health, Nanjing Medical University, Nanjing 211166 China;*
[3]*School of Public Health, Nanjing Medical University, Nanjing 211166, China;*
[4]*The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China*

Received October 25, 2021; accepted April 22, 2022; published online June 14, 2022

Citation: Hu, Z., Yin, Y., Wang, K., Xu, M., Ding, C., Song, Y., Yi, C., Li, J., Yi, Y., and Peng, Z. (2022). Impact of inactivated COVID-19 vaccines on viral shedding in B.1.617.2 (Delta) variant-infected patients. Sci China Life Sci 65, 2556–2559. https://doi.org/10.1007/s11427-021-2115-7

Dear Editor,

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) has waged a global pandemic. As of April 15, 2022, more than 500 million cases of COVID-19 had been reported, with more than 6 million deaths. The ultimate arsenal to fight against this pandemic is highly effective vaccines (Bok et al., 2021; Sadarangani et al., 2021). Clinical trials and real-world evidence have demonstrated that COVID-19 vaccines could reduce the risk of infection, and protect against severe illness and death ensuing breakthrough infection (Bok et al., 2021; Lu et al., 2020; Sadarangani et al., 2021). SARS-COV-2 can be detected by many methods, including antigen detection, nucleic acid test, and viral culture. Among them, nucleic acid test (such as reverse transcription polymerase chain reaction, RT-PCR) is most preferred, because it is more sensitive than antigen test, and less labor-intensive than viral culture. However, little is known regarding whether vaccines influence viral kinetics during the course of COVID-19 disease.

In July and August, 2021, a local COVID-19 epidemic associated with SARS-CoV-2 B.1.617.2 (Delta) variant broke out in Jiangsu, China. A total of 374 patients were included in the analysis, involving 115 (30.7%) unvaccinated, 74 (19.8%) partially vaccinated, and 185 (49.5%) fully vaccinated. The patients received 444 vaccination shots, including 319 of CoronaVac (Sinovac Biotech, Beijing, China), 124 of BBIBP-CorV (Sinopharm, Beijing, China), 1 of KCONVAC (BioKangtai, Shenzhen, China). Of studied patients, 147 (39.3%) were male. The median age was 50 (IQR: 39–65) years, ranging from 18 years to 84 years. Comorbidities presented in 106 (28.3%) patients, the most common being hypertension. Patients tended to be early hospitalized. The median time from disease onset to hospitalization was 2.00 (IQR: 1.00–4.00) days. At the time of admission, about half of the patients displayed positive SARS-COV-2 IgG antibodies (targeting the spike receptor-binding domain). The median Ct value of SARS-COV-2 PCR was 20.0 (IQR: 16.0–24.8) for the N gene (Table S1 in Supporting Information). Other clinical baseline characteristics are detailed in (Table S1 in Supporting Information). At the time of admission, only 2 (<1%) patients had severe/critical COVID-19. During hospitalization, additional 18 (4.8%) showed aggravation to severe/critical COVID-19 after a median of 4 (IQR: 3–6) days. The proportions of severe/critical COVI-19 in early and delayed viral clearance groups (5.5% vs. 5.0%; χ^2=0.03; P=0.858) were similar. Short-course and low-dosage corticosteroids were given to 4

†Contributed equally to this work
*Corresponding authors (Zhihang Peng, email: zhihangpeng@njmu.edu.cn; Yongxiang Yi, email: ian0126@126.com)

(1.1%) patients. All the patients recovered, with no death during hospitalization.

In univariable analysis, odds of early viral clearance was higher in fully vaccinated patients (OR: 2.08; 95%CI: 1.24–3.58; P=0.006), but not in partially vaccinated patients (OR: 1.54; 95%CI: 0.80–2.97; P=0.196). The effect of vaccination in promoting early viral clearance was further evaluated after adjusting for factors affecting the clinical course of COVID-19 and the timing of viral shedding, such as gender, age, comorbidities and viral load at admission (Cevik et al., 2021). Since viral load is influenced by the duration of the disease (Badu et al., 2021; Zhang et al., 2021), the multivariable analysis also included the variable of time from disease onset to admission. After adjusted for those confounding factors, full vaccination was still significantly associated with early viral clearance (adjusted OR: 2.23; 95% CI: 1.17–4.35; P=0.017) (Table S2 in Supporting Information).

As above-mentioned, full vaccination, not partial vaccination, favored early viral clearance. To mitigate the effect of infection-increased SARS-COV-2 IgG levels, the patients who had suffered the disease for more than 5 days were excluded from analysis. As expected, fully vaccinated patients had much a higher baseline SARS-COV-2 IgG level than unvaccinated patients (Figure 1A). The proportions of SARS-COV-2 IgG seroconversion were 6.9% (95%CI: 1.5%–12.3%), 32.3% (95%CI: 20.6%–44%), and 81.4% (95%CI: 75.2%–87.6%) in unvaccinated, partially vaccinated and fully vaccinated patients, respectively (P<0.001). Only a low proportion of the unvaccinated patients had detectable SARS-COV-2 IgG antibodies, suggesting that Delta variant infection was not likely to induce prominent IgG antibodies within 5 days after onset. Therefore, a higher SARS-COV-2 IgG antibody level at admission in fully vaccinated patients might not be related to recent infection with Delta variant, but could reflect a pre-existing immune protection due to vaccination. The duration of viral shedding decreased as the dose of vaccines increased (median [IQR] of 26 [IQR: 22–30], 25 [IQR: 21–29] and 24[IQR: 19–29) in unvaccinated, partially vaccinated, and fully vaccinated patients, respectively; P=0.031). Fully vaccinated patients who achieved early viral clearance had a much higher SARS-COV-2 IgG antibody level (Figure 1B). When fully vaccinated patients were further categorized into three groups based on baseline SARS-COV-2 IgG levels (negative, S/CO<1; low level, S/CO: 1–10; high level, S/CO>10), the duration of viral shedding was substantially reduced in patients with high baseline SARS-COV-2 IgG levels, compared with that in unvaccinated patients (P<0.001 in Figure 1C, P<0.001 in Figure 1D). However, the durations of viral shedding were similar between unvaccinated patients and fully vaccinated patients with negative or low-level baseline SARS-COV-2 IgG (P>0.05; Figure 1D). A Spearman correlation coefficient test was then performed for fully vaccinated patients with positive SARS-COV-2 IgG, to assess the association between baseline SARS-COV-2 IgG level and the duration of viral shedding. As shown in Figure 1E, there was a significant negative correlation between them (r=–0.393, P<0.001).

IgM antibodies appear earlier than IgG antibodies, and may be an ideal marker of recent infection. In our study, at the time of admission, the seroconversion rate of SARS-COV-2 IgM antibodies was similar to that of SARS-COV-2 IgG antibodies in unvaccinated patients (6.9% vs. 6.9%; P=1.0). The finding again suggested that little infection-related antibody responses existed at admission, probably because of early hospitalization of our patients. The higher SARS-COV-2 IgM antibodies levels in partially and fully vaccinated patients could be, to some extent, associated with vaccination (Figure 1F). Partial vaccination substantially increased the seroconversion rate of the SARS-COV-2 IgM antibodies (21.5% vs. 6.9 %; χ^2=6.98; P=0.008). However, there was no further increase in IgM antibody seroconversion rate in fully vaccinated patients (25.6% vs. 21.5%; χ^2=0.42; P=0.518). In patients with negative SARS-COV-2 IgM antibodies, the interval from the last vaccination shot to admission was longer, as compared to that in patients with positive tests (median 87.5, IQR: 47–114 vs. median, 47.5, IQR: 36.0–92.8; P=0.001; Figure 1G). These findings suggested that the unsatisfactory SARS-COV-2 IgM antibody level in fully vaccinated patients might be associated with the decay of SARS-COV-2 IgM antibodies. In those patients with positive SARS-COV-2 IgM antibodies, the duration of viral shedding was relatively shorter (P=0.013, Figure 1H).

SARS-COV-2 viral loads in our study were not significantly different among unvaccinated, partially vaccinated and fully vaccinated patients (median Ct values of 19, 20 and 18, respectively; P=0.078; Figure 1I). Since SARS-COV-2 antibody levels varied in vaccinated patients, we then evaluated the viral loads stratified by antibody levels. In either partially or fully vaccinated patients, SARS-COV-2 viral load was significantly lower in patients with high SARS-COV-2 IgG antibody levels (P=0.007 and P<0.001, respectively; Figure 1J). A moderate correlation existed between Ct value and SARS-COV-2 IgG antibody level (Spearman r=0.423 and 0.436; P<0.001 and <0.001 in partially and fully vaccinated patients, respectively; Figure 1K and 1L). As shown in Figure 1M, among the partially vaccinated patients, those with positive SARS-COV-2 IgM antibodies had a much lower viral load (median Ct values of 26 and 19 in IgM positive and negative patients, respectively; P=0.003). Also, there was a moderate correlation between Ct value and SARS-COV-2 IgM antibody level in partially vaccinated patients (Spearman r=0.468; P<0.001; Figure 1N). In fully vaccinated patients, a substantial reduction in viral load was not seen in SARS-COV-2 IgM seropositive patients (median

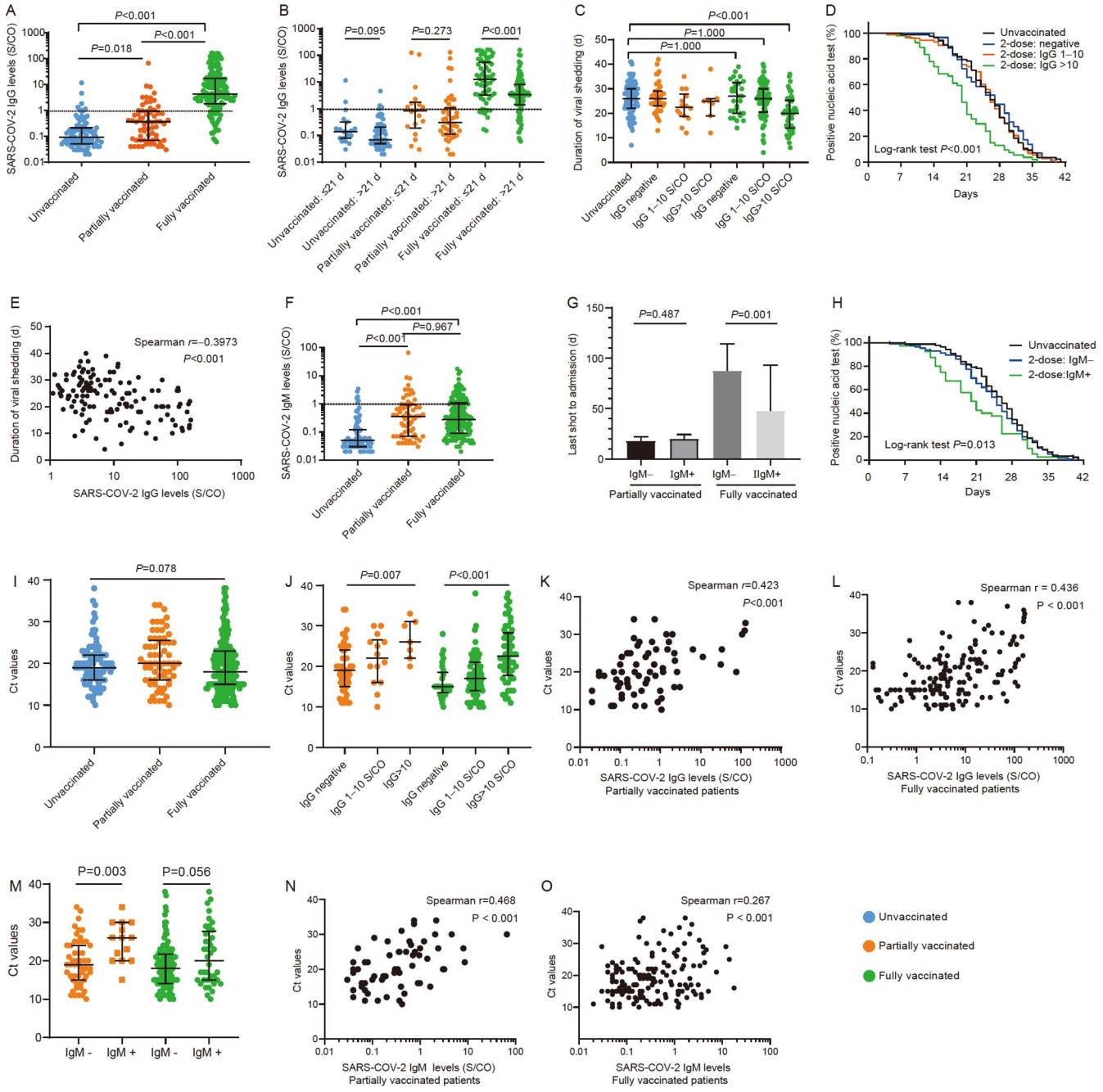

Figure 1 Viral shedding at different SARS-COV-2 antibody levels. At admission, fully vaccinated patients had much higher baseline SARS-COV-2 receptor-binding domain (RBD) IgG levels than partially vaccinated and unvaccinated patients (A). Within the fully vaccinated patients, patients with early viral clearance had much higher SARS-COV-2 IgG antibody levels (B), and substantial reduction in the duration of viral shedding was only observed in patients with high baseline SARS-COV-2 IgG levels [signal/cut-off (S/CO) value 10] (C and D). There was a significant negative correlation between baseline SARS-COV-2 IgG levels and the duration of viral shedding (E). Although SARS-COV-2 RBD IgM antibody levels were higher in vaccinated patients than that in unvaccinated patients, no significant difference of SARS-COV-2 RBD IgM antibody levels was observed between partially and fully vaccinated patients (F). Among the fully vaccinated patients, SARS-COV-2 RBD IgM antibody negative patients had longer time intervals from the last vaccination shot to admission as compared to SARS-COV-2 RBD IgM antibody positive patients (G), and viral decay was faster in SARS-COV-2 RBD IgM positive patients (H), viral loads (as represented by cycle threshold [Ct] value from quantitative reverse transcription polymerase chain reaction) were similar among unvaccinated, partially vaccinated and fully vaccinated patients (I). Within the partially vaccinated or fully vaccinated patients, SARS-COV-2 viral loads were significantly lower in patients with high SARS-COV-2 receptor-binding domain (RBD) IgG antibody levels (J). There were moderate correlations between Ct values and SARS-COV-2 RBD IgG antibody levels in partially as well as fully vaccinated patients (K and L). Although, in partially vaccinated patients, viral loads were lower in SARS-COV-2 IgM antibody positive patients than that in SARS-COV-2 IgM antibody negative patients, there was no significantly different of viral loads in fully vaccinated patients categorized by SARS-COV-2 RBD IgM antibody levels (M). There was moderate correlation between Ct values and SARS-COV-2 RBD IgM antibody levels in partially vaccinated patients (N), however, only weak correlation existed in fully vaccinated patients (O).

Ct values of 20 and 18 in IgM positive and negative patients, respectively; P=0.056; Figure 1M). There was only a weak correlation between Ct value and SARS-COV-2 IgM antibody level in fully vaccinated patients (Spearman r=0.267; P<0.001; Figure 1O). For the above-mentioned reasons, compared with SARS-COV-2 IgM antibodies, SARS-COV-2 IgG antibodies were more suitable for evaluating vaccination-related immune protection.

Our study has several limitations. First, like the majority of previous studies (Bongiovanni et al., 2021; Zhou et al., 2020), viral load was measured by molecular method and viral culture was not performed. Second, vaccine efficacy was evaluated by using SARS-COV-2 RBD antibodies. Data regarding the SARS-COV-2 neutralizing antibody level, a sensitive index of immune protection, was not available. Since SARS-COV-2 RBD antibody level is strongly correlated with SARS-COV-2 neutralizing antibody levels (Iyer et al., 2020), RBD antibody could be an alternative to neutralizing antibody.

In conclusion, full vaccination with inactivated vaccines can promote early viral clearance. The magnitude of protection against prolonged viral shedding may correlate with vaccine-induced anti-viral immunity. The findings in our study strongly suggest that vaccine immune pressure influences viral RNA dynamic. It is of great importance to explore whether vaccine immune pressure may have similar impact on infectious viral shedding. From a virological perspective, our study provides additional evidence to support wider full vaccination.

Compliance and ethics *The authors declare that they have no conflict of interest. This study was approved by the ethics committee of the Second Hospital of Nanjing (2020-LS-ky003). Written informed consent was waived by the Ethics Commission.*

Acknowledgements *This work was supported by the National Natural Science Foundation of China (82073673), the National Science and Technology Major Project of China (2018ZX10715002-004-002, 2018ZX10713001-001), the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD), Key Research and Development Program of Department of Health of Jiangsu (ZDB2020036), and Project of Nanjing Infectious Disease Clinical Medical Center Construction (NA2021062071).*

References

Badu, K., Oyebola, K., Zahouli, J.Z.B., Fagbamigbe, A.F., de Souza, D.K., Dukhi, N., Amankwaa, E.F., Tolba, M.F., Sylverken, A.A., Mosi, L., et al. (2021). SARS-COV-2 viral shedding and transmission dynamics: Implications of WHO COVID-19 discharge guidelines. Front Med 8, 648660.

Bok, K., Sitar, S., Graham, B.S., and Mascola, J.R. (2021). Accelerated COVID-19 vaccine development: Milestones, lessons, and prospects. Immunity 54, 1636–1651.

Bongiovanni, M., Bini, F., Giuliani, G., and Gianturco, L. (2021). Insight into the reason of prolonged viral rna shedding in patients with COVID-19 infection. J Infect 82, e13–e14.

Cevik, M., Tate, M., Lloyd, O., Maraolo, A.E., Schafers, J., and Ho, A. (2021). SARS-COV-2, SARS-COV, and MERS-COV viral load dynamics, duration of viral shedding, and infectiousness: A systematic review and meta-analysis. Lancet Microbe 2, e13–e22.

Lu, L., Zhang, H., Zhan, M., Jiang, J., Yin, H., Dauphars, D.J., Li, S.Y., Li, Y., and He, Y.W. (2020). Antibody response and therapy in COVID-19 patients: what can be learned for vaccine development? Sci China Life Sci 63, 1833–1849.

Iyer, A.S., Jones, F.K., Nodoushani, A., Kelly, M., Becker, M., Slater, D., Mills, R., Teng, E., Kamruzzaman, M., Garcia-Beltran, W.F., et al. (2020). Persistence and decay of human antibody responses to the receptor binding domain of SARS-CoV-2 spike protein in COVID-19 patients. Sci Immunol 5.

Sadarangani, M., Marchant, A., and Kollmann, T.R. (2021). Immunological mechanisms of vaccine-induced protection against COVID-19 in humans. Nat Rev Immunol 21, 475–484.

Zhang, N., Gong, Y., Meng, F., Shi, Y., Wang, J., Mao, P., Chuai, X., Bi, Y., Yang, P., and Wang, F. (2021). Comparative study on virus shedding patterns in nasopharyngeal and fecal specimens of COVID-19 patients. Sci China Life Sci 64, 486–488.

Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X., et al. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in wuhan, china: A retrospective cohort study. Lancet 395, 1054–1062.

SUPPORTING INFORMATION

The supporting information is available online at https://doi.org/10.1007/s11427-021-2115-7. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.