Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
The impacts of vaccination status and host factors during early infection on SARS-CoV-2 persistence: a retrospective single-center cohort study

Xiangxiang Tian\textsuperscript{a,c,e,g,1}, Yifan Zhang\textsuperscript{a,c,e,1}, Wanhai Wang\textsuperscript{c}, Fang Fang\textsuperscript{d}, Wenhong Zhang\textsuperscript{e,f}, Zhaqin Zhu\textsuperscript{a,1}, Yanmin Wan\textsuperscript{b,c,f,*}

\textsuperscript{a} Department of Laboratory Medicine, Shanghai Public Health Clinical Center, Fudan University, Shanghai 201508, China
\textsuperscript{b} Department of Radiology, Shanghai Public Health Clinical Center, Fudan University, Shanghai 201508, China
\textsuperscript{c} Clinical Laboratory, The First Affiliated Hospital of Zhengzhou University, Key Laboratory of Laboratory Medicine of Henan Province, Zhengzhou 450052, China
\textsuperscript{d} Shanghai Public Health Clinical Center, Fudan University, Shanghai 201508, China
\textsuperscript{e} Department of Infectious Diseases, Shanghai Key Laboratory of Infectious Diseases and Biosafety Emergency Response, National Medical Center for Infectious Diseases, Huashan Hospital, Fudan University, Shanghai 200040, China
\textsuperscript{f} State Key Laboratory of Genetic Engineering, School of Life Science, Fudan University, Shanghai 200000, China
\textsuperscript{g} Department of Clinical Laboratory, The First People’s Hospital of Shangqiu, Shangqiu 476000, China

A R T I C L E   I N F O

Keywords:
COVID-19
Inactivated vaccine
Laboratory variables
mRNA vaccine
Viral RNA shedding

A B S T R A C T

Background: Viral persistence is a crucial factor that influences the transmissibility of SARS-CoV-2. However, the impacts of vaccination and physiological variables on viral persistence have not been adequately clarified.

Methods: We collected the clinical records of 377 COVID-19 patients, which contained unvaccinated patients and patients received two doses of an inactivated vaccine or an mRNA vaccine. The impacts of vaccination on disease severity and viral persistence and the correlations between 49 laboratory variables and viral persistence were analyzed separately. Finally, we established a multivariate regression model to predict the persistence of viral RNA.

Results: Both inactivated and mRNA vaccines significantly reduced the rate of moderate cases, while the vaccine related shortening of viral RNA persistence was only observed in moderate patients. Correlation analysis showed that 10 significant laboratory variables were shared by the unvaccinated mild patients and mild patients inoculated with an inactivated vaccine, but not by the mild patients inoculated with an mRNA vaccine. A multivariate regression model established based on the variables correlating with viral persistence in unvaccinated mild patients could predict the persistence of viral RNA for all patients except three moderate patients inoculated with an mRNA vaccine.

Conclusion: Vaccination contributed limitedly to the clearance of viral RNA in COVID-19 patients. While, laboratory variables in early infection could predict the persistence of viral RNA.

1. Introduction

Real world studies suggest that the implementing of vaccination have dramatically reduced the rates of SARS-CoV-2 infection and SARS-CoV-2 related hospitalization, admission to intensive care unit and death [1–3]. In addition, retrospective estimations have also suggested that vaccines were effective at preventing the transmission of both the Alpha\textsuperscript{[4,5]} and the Delta variants\textsuperscript{[6]}. It is believed that the vaccine mediated reduction of transmission relies on the prevention of infection, while the effect of vaccines in preventing onward transmission after breakthrough infections has not been adequately clarified.

It is speculated that vaccines may help to restrain the onward transmission of SARS-CoV-2\textsuperscript{[7]} based on observations that COVID-19 vaccination can reduce viral loads in nasal mucosa\textsuperscript{[8–10]}. However, contradictory evidence showed that the viral loads of breakthrough infections after full vaccination were similar with those of unvaccinated individuals\textsuperscript{[11,12]}. More recently, a preprint study carried out in a prison demonstrated that there was no significant difference in the

\textsuperscript{1} Yanmin Wan will handle correspondence at all stages of refereeing and publication.
\textsuperscript{*} Corresponding authors.
\textsuperscript{E-mail addresses:} zhuzhaoqin@shaphc.org (Z. Zhu), yanmin.wan@fudan.edu.cn (Y. Wan).
\textsuperscript{1} Xiangxiang Tian and Yifan Zhang contributed equally to this work.

https://doi.org/10.1016/j.intimp.2022.109534
Received 23 September 2022; Received in revised form 13 November 2022; Accepted 28 November 2022
Available online 30 November 2022
1567-5769/© 2022 Elsevier B.V. All rights reserved.
duration of RT-PCR positivity and the kinetics of Ct values between fully vaccinated participants and those not fully vaccinated [13].

In addition to vaccination status, the onward transmission risk can also be driven directly by factors, such as closeness of social interactions, symptom status, the severity of illness, environment, and time of exposure [14]. Host defense mechanism has been shown to affect susceptibility to infection [15], but its impact on onward transmission has not been clearly elucidated. To reveal the impacts of vaccination status and the host factors during early infection on the potential of onward transmission, in this study, we retrospectively retrieved the clinical records of 377 hospitalized COVID-19 patients and analyzed the correlations between the host variables and the duration of viral RNA shedding. Given that the levels of viral RNA can reflect the shedding of infectious virus [16], factors that associate with pharyngeal viral RNA shedding may serve as indicators for the potential of onward transmission. The findings of this study may provide a rationale to optimize the management of hospitalized COVID-19 patients and the control measures for the pandemic.

2. Materials and methods

2.1. Ethical approval statement

This study was approved by the Research Ethics Review Committee (Ethics Approval Number: YJ-2020-S080-02) of the Shanghai Public Health Clinical Center Affiliated to Fudan University.

2.2. Study design and participants

377 COVID-19 patients hospitalized in Shanghai Public Health Clinical Center during the period from January 2020 to mid-January 2022 were included in this study. The diagnosis and clinical management of COVID-19 patients were conducted following the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia released by National Health Commission & National Administration of Traditional Chinese Medicine [17]. According to the protocol, mild patients refer to those who have mild the clinical symptoms and show no sign of pneumonia. Moderate patients refer to those who have fever and respiratory symptoms and show signs of pneumonia. The demographic and COVID-19 vaccination information were depicted in Table 1. 49 laboratory variables detected at the immediate early stage of infection and the duration of viral RNA shedding were shown in Supplementary Table 1. The duration of viral RNA shedding was defined as the period from the initial nasal swab RT-PCR positivity to the final nasal swab RT-PCR positivity. Patients with hypertension, diabetes, hyperlipidemia and/or chronic obstructive pulmonary disease were excluded.

2.3. SARS-CoV-2 viral RNA detection

Viral RNA extraction was performed using an automatic nucleic acid extractor (Bioperfectus technologies Co., ltd., Jiangsu, China). 2019-nCoV nucleic acid detection kit (Bioperfectus technologies Co., ltd., Jiangsu, China) and ABI 7500 real-time fluorescence quantitative PCR (qPCR) instrument (Thermo Fisher Technology Co., ltd., Shanghai, China) were used to detected SARS-CoV-2 genomic RNA. When the Ct values of both ORF1ab and N gene of 2019-nCoV are ≤ 37 and the amplification curve is ‘S-shaped’, the result is defined as positive. When the Ct values of both genes are > 40 or undetermined, the result is defined as negative. When the Ct value is between 37 ~ 40, the sample would be re-examined.

2.4. Laboratory measurements

All the laboratory tests were carried out following manufacturers’ instructions in the department of laboratory medicine of Shanghai Public Health Clinical Center. All the tests had passed the ISO15189 accreditation. In this study, we retrospectively retrieved the values of 49 laboratory variables (Supplementary Table 1) for each patient, which were measured at a median of 3 days post diagnosis.

2.5. Statistical analysis

Quantitative data were examined for normality using the Shapiro-Wilk test before all downstream analyses except the Chi square test. Means for variables with a normal distribution were compared using the two-tailed parametric t-test and with the two-tailed non-parametric t-test when distributions of data departed from normality. Pearson correlation was used for correlation analyses of normally distributed data and Spearman correlation was used for analyses of non-normally distributed data. Multivariate regression analyses were performed for variables with statistical significance by the correlation analysis. P ≤ 0.05 was considered as statistically significant. All the statistical analyses were conducted using Graphpad Prism 9 (GraphPad Software, USA).

3. Results

3.1. Demographical characteristics of COVID-19 patients

In this study, we retrospectively retrieved the clinical records of 377 COVID-19 patients hospitalized in Shanghai Public Health Clinical Center during the period from January 2020 to mid-January 2022. Among these patients, 165 received two doses of an inactivated vaccine, 41 received two doses of an mRNA vaccine and 171 were not vaccinated (W/O vaccination) (Table 1). The median age was similar across all groups (P = 0.5651), and the mean time since-vaccination of patients inoculated with an inactivated vaccine was comparable with that of patients inoculated with an mRNA vaccine (P = 0.1183) (Table 1). The gender composition of patients inoculated with an mRNA vaccine was significantly different from the other two groups, which contained more female (P = 0.0011) (Table 1), but it did not impact the duration of viral RNA shedding and the severity of disease (Supplementary Fig. 1).
3.2. Vaccines reduced the proportion of moderate cases and shortened the duration of viral RNA shedding among these patients

Compared with unvaccinated patients, patients inoculated with either an inactivated vaccine (19.4 % vs 35.7 %, P = 0.0002) or an mRNA vaccine (7.3 % vs 35.7 %, P = 0.0001) significantly reduced the incidence of moderate cases (Fig. 1A). More interestingly, we found that patients inoculated with an inactivated vaccine showed significantly - shorter duration of viral RNA shedding in moderate patients compared with unvaccinated patients (17, IQR 12.25–19.5 vs 19, IQR 12–24.5, P = 0.0382) and patients inoculated with an mRNA vaccine (17, IQR 12.25–19.5 vs 22.33 ± 4.163, P = 0.0385) (Fig. 1B). However, the vaccines showed no effect on constraining the duration of viral RNA shedding in mild COVID-19 patients (Fig. 1C).

3.3. Common variables that correlated with the duration of viral RNA shedding were found in unvaccinated mild patients and mild patients inoculated with an inactivated vaccine, but not in those inoculated with an mRNA vaccine

As aforementioned, the vaccines failed to constrain the duration of viral RNA shedding in mild COVID-19 patients (Fig. 1C), which implies that vaccine induced immune responses might not play a pivotal role in determining viral persistence in these patients. To identify physiological variables that are associated with the duration of viral RNA shedding in the mild COVID-19 patients, we performed correlation analyses between the duration of viral RNA shedding and 49 laboratory variables detected at the immediate early stage of infection. Our data showed that 16 variables in unvaccinated patients (Fig. 2A) and 15 variables in patients inoculated with an inactivated vaccine (Fig. 2B) correlated with the duration of viral RNA shedding, respectively. Of note, 10 variables were shared by these two groups of patients, including 3 positively correlated variables (Fibrinogen concentration, Monocyte count and IL-17 concentration) and 7 negatively correlated variables (Neutrophil, Eosinophil, Basophil, CD4+, CD8+, CD19+ and CD16+CD56+ cell counts). In contrast, in patients inoculated with an mRNA vaccine, only one variable (eGFR, estimated glomerular filtering rate) was found to correlate negatively with the duration of viral RNA shedding (Fig. 2C). Next, we compared the laboratory variables among the three groups of mild COVID-19 patients and found that inoculations with an inactivated vaccine or an mRNA vaccine influenced the laboratory parameters differentially (Supplementary Table 1). Patients inoculated with an mRNA vaccine mounted highest median IL-8 and IL-17 responses at the immediate early stage of infection (Supplementary Table 1).

3.4. Variables correlating with the duration of viral RNA shedding in unvaccinated mild patients could predict the duration of viral RNA shedding in all patients except the moderate patients inoculated with an mRNA vaccine

Although multiple individual parameters were found to correlate significantly with the duration of viral RNA shedding, the correlation coefficients were low (|r|<0.5) (Fig. 2), suggesting that the correlations were relatively weak. This notion was supported by the results of univariate logistic regression analyses, which showed that no individual variable could reliably discriminate between the short duration of viral RNA shedding (<14 days) and the long shedding duration (>14 days) in unvaccinated mild patients (AUC < 0.80) (Supplementary Fig. 2). The count of CD19+ B cell is of the highest discriminating efficiency (AUC = 0.7556) followed by the count of CD4+ T cell (AUC = 0.7261) (Supplementary Fig. 2). To further characterize the relationships between host factors and viral persistence, we performed multivariate logistic regression analyses exploiting the significant factors identified in the correlation analyses for unvaccinated mild patients. Our results showed that the selected laboratory variables discriminated between the short (<14 days) and the long (>14 days) viral RNA shedding duration quite well for all the three groups of mild COVID-19 patients. The area under the ROC curve (AUC) for unvaccinated patients, patients inoculated with an inactivated vaccine and patients inoculated with an mRNA vaccine were 0.9231, 0.8365 and 0.9508, respectively (Fig. 3). Moreover, we found that this multivariate regression model could also predict the duration of viral RNA shedding in moderate COVID-19 patients. The AUC for unvaccinated moderate patients and moderate patients inoculated with an inactivated vaccine were 0.9110 and 0.9514, respectively (Fig. 4). Due the limited sample size (only three patients), the multivariate regression analysis could not be applied to moderate patients inoculated with an mRNA vaccine.

![Fig. 1. The impacts of vaccination on COVID-19 clinical manifestation and the duration of viral RNA shedding.](image-url) (A) The proportions of mild and moderate COVID-19 cases were compared among unvaccinated patients and patients inoculated with an inactivated vaccine or an mRNA vaccine. (B) Comparisons of the duration of viral RNA shedding among moderate COVID-19 patients. (C) Comparisons of the duration of viral RNA shedding among mild COVID-19 patients. Statistical analyses were performed by the method of non-parametric t-test.
4. Discussion

An important factor that influences the transmission of SARS-CoV-2 is the period of transmissibility, which may be influenced by many factors. To identify these factors, detections of live virus and viral RNA are frequently used as indicators of transmissibility, of which the live virus culture is thought to be more relevant to the transmissibility of SARS-CoV-2 infections [18–20]. However, the culture of live virus is
time-consuming and might be affected by specimen qualities and the sensitivities of laboratory methods. Hence, as an alternative solution, the measurement of viral RNA shedding remains to be an important criterion for the diagnosis of COVID-19 and the discharge of hospitalized patients [21].

Multiple factors have been found to associate with prolonged viral RNA shedding in previous studies, such as old age [22], compromised immune status [23], treatment with corticosteroids [24–26] and disease severity [27,28]. Meanwhile, biological sex and comorbidities, such as hypertension and diabetes, were found not to associate with the viral RNA shedding [29–31]. Unlike most previous works, our current study investigated the impacts of vaccination status and multiple laboratory variables during early infection on the duration of viral RNA shedding.

First of all, we compared the ratios of moderate COVID-19 cases among unvaccinated patients and patients fully vaccinated with either an inactivated vaccine or an mRNA vaccine. Our data showed that both the inactivated and the mRNA vaccines significantly reduced the incidence of moderate cases, which is in consistence with the observation of a previous real-world study [32]. Next, we compared the duration of viral RNA shedding between unvaccinated and fully vaccinated patients. Quite unexpectedly, our results showed that vaccination significantly shortened the duration of virus shedding in moderate patients but not in mild patients, suggesting that vaccine induced specific immune responses did not contribute significantly to constraining viral persistence in mild patients. We were not able to elaborate the underlying mechanism in this retrospective study. However, as previous studies suggested that more severe COVID-19 could usually evoke stronger host immune responses [33,34], we speculate that the memory immune responses established by vaccination could be more efficiently activated in moderate patients, which may control the in vivo virus replication better.

Next, to characterize host factors that may affect viral persistence in mild COVID-19 patients, we retrieved 49 laboratory variables which were detected at the immediate early stage after infection (at a median of 3 days post diagnosis). Correlation analyses showed that the plasma levels of IL-17, fibrinogen and the counts of peripheral leucocytes were associated with the duration of viral RNA shedding in both unvaccinated patients and patients inoculated with an inactivated vaccine. Elevated levels of proinflammatory cytokines and lymphopenia have been demonstrated to be associated with prolonged viral RNA shedding by previous studies [35–37]. Here, we further showed that the counts of T, B, NK, neutrophil and eosinophil were negatively associated with the duration of viral RNA shedding, while the count of monocyte was

Fig. 4. Variables correlating with viral persistence in unvaccinated mild patients could discriminate between the short (≤14 days) and the long (>14 days) duration of viral RNA shedding for moderate COVID-19 patients. A multivariate regression model constructed using factors identified in unvaccinated mild patients discriminated between the short and the long duration of viral RNA shedding for unvaccinated moderate patients (A) and moderate patients inoculated with an inactivated vaccine (B).
positively associated with the duration of viral RNA shedding. More intriguingly, our data showed that all the significant individual variables identified in unvaccinated patients and patients inoculated with an inactivated vaccine were not significantly associated with the duration of viral RNA shedding in patients inoculated with an mRNA vaccine. This phenomenon implies that the mRNA vaccine may have unique impacts on host responses after break through infection. And these impacts might be deleterious, because the median duration of viral RNA shedding of patients inoculated with an mRNA vaccine tended to be longer than those of unvaccinated patients and patients inoculated with an inactivated vaccine. Insight into the underlying mechanisms will help to improve our understanding of the biological effect of mRNA vaccine.

At the end of this study, we established a multivariate regression model using the individual factors correlating with the duration of viral RNA shedding in unvaccinated mild patients and found that the model could be applied to all groups of patients, including the mild patients inoculated with an mRNA vaccine and the moderate patients. This finding suggests that despite of the impacts of vaccination status and the difference of disease severity, the combined effect of host factors on viral persistence remains stable.

Several limitations of the present study should be noted. First, antigen-specific immune responses were not detected in this retrospective work. Nonetheless, we speculate that the vaccine induce immunities might not be able to constrain viral RNA shedding in mild COVID-19 patients, since both an inactivated vaccine and an mRNA vaccine failed to shorten the duration of viral RNA shedding in these patients. Second, although a previous study showed that viral RNA load (>10^7 copies/mL) is an independent risk factor for live virus shedding [38], the detection viral RNA might not always indicate the presence of live viruses. Further investigations are necessitated to characterize host factors that associate with the shedding of viable viruses. Third, most cases enrolled in this study were infected by either the D614G variant or the Delta variant, but we were not able to define the infected variant for each case. Therefore, the impact of viral factor on the duration of viral RNA shedding is out-of-scope for this study.

Despite of these limitations, our study showed for the first time that COVID-19 vaccines contributed to the clearance of viral RNA in moderate cases, while failed to shorten the duration of viral RNA shedding in mild patients. Moreover, we identified a set of laboratory variables in early infection that could predict the persistence of viral RNA. These findings may serve as a rationale to optimize the control measures for COVID-19 pandemic.

5. Conclusions

Our study showed that COVID-19 vaccines contributed to the clearance of viral RNA in moderate cases, but not in mild patients. Moreover, we identified a set of laboratory variables in early infection that could predict the persistence of viral RNA.

Data availability

All the data generated during the current study are included in the manuscript.

CRedit authorship contribution statement

Xiangxian Tian: Investigation, Writing – original draft. Yifan Zhang: Software, Writing – original draft. Wanhai Wang: Methodology, Supervision. Fang Fang: Validation. Wenhong Zhang: Writing – review & editing. Zhaqin Min: Methodology, Validation, Supervision. Yanmin Wan: Funding acquisition, Methodology, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgments

This work was supported by a grant from the National Natural Science Foundation of China [81971559, 32270986], a grant from the major project of Study on Pathogenesis and Epidemic Prevention Technology System by the Ministry of Science and Technology of China [2021YFC2302500] and a grant from the Science and Technology Commission of Shanghai Municipality [21NL2600100]. We thank Dr. Liqiu Jia and Ms. Jing Wang for their help in retrieving the clinical records of the COVID-19 patients.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2022.109534.

References

[1] Q. Liu, C. Qin, M. Liu, J. Liu, Effectiveness and safety of SARS-CoV-2 vaccine in real-world studies: a systematic review and meta-analysis, Infectious Diseases of Poverty 10 (1) (2021) 132.
[2] C. Zheng, W. Shao, X. Chen, B. Zhang, G. Wang, W. Zhang, Real-world effectiveness of COVID-19 vaccines: a literature review and meta-analysis, International Journal of Infectious diseases : IJID : official publication of the International Society for, Infect. Dis. 114 (2022) 252–260.
[3] D. Hungerford, N.A. Caniff, Real world effectiveness of covid-19 vaccines 374 (2021), n2034.
[4] A.S.V. Shah, C. Gibben, J. Bishop, P. Hanlon, D. Caldwell, R. Wood, M. Reid, J. McMenamin, D. Goldberg, D. Stockton, S. Hutchinson, C. Robertson, P. M. McKeigue, H.M. Colbourn, D.A. McAllister, Effect of vaccination on transmission of SARS-CoV-2, N. Engl. J. Med. 385 (18) (2021) 1718–1720.
[5] R.J. Harris, J.A. Hall, A. Zaidi, N.J. Andrews, J.K. Dunbar, G. Dabrera, Effect of vaccination on household transmission of SARS-CoV-2 in England, N. Engl. J. Med. 385 (8) (2021) 759–760.
[6] D.W. Eyre, D. Taylor, M. Purver, D. Chapman, T. Fowler, K.B. Pouwels, A.S. Walker, T.E. Peto, The impact of SARS-CoV-2 vaccination on Alpha & Delta variant transmission, (2021), no. 28.21264260.
[7] A. Vitiello, F. Ferrara, V. Troiano, R. La Forza, COVID-19 vaccines and decreased transmission, (2021) 2116.01548.
[8] E. Callaway, Delta coronavirus variant: scientists brace for impact, Nature 595 (7865) (2021) 17–18.
[9] M. Levine-Tiefenbrun, I. Yelin, R. Katz, E. Herzel, Z. Golan, L. Schreiber, T. Wolf, V. Nadler, A. Ben-Tov, J. Kuint, S. Gazit, T. Patalon, G. Chodick, R. Kishony, Initial report of decreased SARS-CoV-2 viral load after inoculation with the BNT162b2 vaccine, Nat. Med. 27 (5) (2021) 790–792.
[10] M. Levine-Tiefenbrun, I. Yelin, H. Alapi, R. Katz, E. Herzel, J. Kuint, S. Gazit, T. Patalon, G. Chodick, R. Kishony, Initial report of decreased SARS-CoV-2 viral load after vaccination and booster with BNT162b2, Nat. Med. 27 (12) (2021) 2108–2110.
[11] K.B. Pouwels, E. Pritchard, M. Stoesser, D.W. Eyre, K.-D. Vihta, T. House, J. Hay, J.L. Bell, J.N. Newton, J. Farrar, D. Crook, D. Cook, E. Bourlee, R. Studley, T. Petö, J. Diamond, A.S. Walker, C.-L.S. Team, Impact of Delta on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK, (2021) 2021.08.18.21262237.
[12] K.K. Riemersma, B.E. Grogan, A. Kita-Yarbo, P.J. Halffman, H.E. Segallof, A. Kocharian, K.R. Florek, R. Westergaard, A. Bateman, G.E. Jeppson, Y. Kawaoaka, D. H. O’Connor, T.C. Friedrich, K.M. Grande, Shedding of Infectious SARS-CoV-2, (2021) 2021.07.31.21261387.
[13] J. Salvatore, C.C. Lee, S. Snowdon, D.W. McCormick, L. Nicolai, K. Knipe, T. Dixon, R. Banta, I. Ogle, C. Young, C. Dusseau, S. Salomonson, C. Ogden, E. Godwin, T. Ballom, T. Ross, N.T. Wynn, E. David, T.K. Bessey, G. Kim, S. Suppiah, A. Tamin, J.L. Harcourt, M. Sheth, L. Lowe, H. Browne, J.E. Tate, H.L. Kirking, L.M. Hagan, Transmission potential of SARS-CoV-2 and attributable number of infections from vaccinated and unvaccinated persons infected with the SARS-CoV-2 Delta variant in a federal prison, July—August 2021, (2021) 2021.11.21265796.
[14] M. Cevik, S.D. Baral, Networks of SARS-CoV-2 transmission, Science 373 (6551) (2021) 162–163.
[15] M. Cevik, J.L. Marcus, C. Buckee, T.G. Smith, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission dynamics should inform policy, Clin Infect Dis 73 (Suppl 2) (2021) S170–S176.
[16] K. Takahashi, M. Ishikane, M. Ujiie, N. Okumura, T. Sato, M. Nagashima, A. Moriya, M. Suzuki, M. Hojo, T. Kanno, S. Saito, N. Yamato, T. Suzuki, N. Ohmagari, Duration of infectious virus shedding by SARS-CoV-2 Delta variant in a federal prison, July—August 2021, (2021) 2021.11.21265796.
Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7), Chinese medical journal 133(9) (2020) 1087-1095.

V. Manzelli, G. Cataldi, A. Fumagalli, C. Dacianza, L. Pace, D. Copilotta, P. Tondo, R. De Nittis, V. Rondinone, L. Serrecchia, A. Parisi, D. Galante, S. Lo Caputo, T.A. Santantonio, D. Moschetta, V. Dattoli, A. Fasanella, M.P. Foschino Barbaro, Real time PCR and culture-based virus isolation test in clinically recovered patients is the still subject for SARS-CoV-2? J. Clin. Med. 10 (2) (2021) 309,

C.G. Huang, K.-M. Lee, J.-M. Hsiao, S.-L. Yang, P.-N. Huang, Y.-C. Gong, T.-T. Hsieh, P.-W. Huang, Y.-J. Liu, Y.-C. Tsao, S.-S. Shih, A.J. McAdam, Culture-based virus isolation to evaluate potential infectivity of clinical specimens tested for COVID-19, J. Clin. Microbiol. 58 (8) (2020).

T. Jefferson, E.A. Spencer, J. Breray, C. Henehan, Viral cultures for coronavirus disease 2019 infection: A systematic review, Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America 73 (11) (2021) e3884-e3899.

Y.H. Jin, Q.Y. Zhan, Z.Y. Peng, X.O. Ren, X.T. Yin, L. Cai, Y.F. Yuan, J.R. Yue, X. Tian et al., Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7), Chinese medical journal 133(9) (2020) 1087-1095.

C. Gao, L. Zhu, N. Gong, B. Liu, X. Lu, D. Chen, S. Chen, H. Shu, K. Ma, X. Xu, Z. Guo, E. Lu, D. Chen, Q. Ge, C.J. Jiang, X. Wei, W. Zhang, G. Chen, Z. Chen, Coronavirus disease 2019 pneumonia in immunosuppressed renal transplant recipients: a summary of 10 confirmed cases in Wuhan, China, European Urology 77 (6) (2020) 748-754.

F. Hu, G. Yin, Y. Chen, J. Song, M. Ye, J. Liu, C. Chen, Y. Song, X. Tang, Y. Zhang, Corticosteroid, oseltamivir and delayed admission are independent risk factors for prolonged viral shedding in patients with Coronavirus Disease 2019, Clin. Respir. Med. 8 (2020) 1067-1075.

W. Liu, Y. Liu, Z. Xu, T. Jiang, Y. Kang, G. Zhi, Z. Chen, Clinical characteristics and predictors of the duration of SARS-CoV-2 viral shedding in 14000 healthcare workers, J. Intern. Med. 288 (6) (2020) 725-736.

L. Qi, Y. Yang, D. Jiang, C. Tu, L. Wan, X. Chen, Z. Li, Factors associated with the duration of viral shedding in adults with COVID-19 outside of Wuhan, China: a retrospective cohort study, International Journal of Infectious Diseases: IJD (2021) 14-11 (2020) 1067-1075.

L. Qi, Y. Yang, D. Jiang, C. Tu, L. Wan, X. Chen, Z. Li, Factors associated with the duration of viral shedding in adults with COVID-19 outside of Wuhan, China: a retrospective cohort study, International Journal of Infectious Diseases: IJD (2021) 14-11 (2020) 1067-1075.

C. Zhou, T. Zhang, X. Sun, S. Yu, J. Sheng, Y. Shi, H. Zhao, Impact of age on severe acute respiratory coronavirus virus 2 (SARS-CoV-2): Review of literature, (2020) 2020.07.28.20163873.