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Reactogenicity and immunogenicity of heterologous prime-boost immunization with COVID-19 vaccine

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A B S T R A C T

Background: The objective of the present work was to assess the reactogenicity and immunogenicity of heterologous COVID-19 vaccination regimens in clinical trials and observational studies.

Methods: PubMed, Cochrane Library, Embase, MedRxiv, BioRxiv databases were searched in September 29, 2021. The PRISMA instruction for systemic review was followed. Two reviewers independently selected the studies, extracted the data and assessed risk of bias. The quality of studies was evaluated using the New Castle-Ottawa and Cochrane risk of instrument. The characteristics and study outcome (e.g., adverse events, immune response, and variant of concern) were extracted.

Results: Nineteen studies were included in the final data synthesis with 5 clinical trials and 14 observational studies. Heterologous vaccine administration showed a trend toward more frequent systemic reactions. However, the total reactogenicity was tolerable and manageable. Importantly, the heterologous prime-boost vaccination regimens provided higher immunogenic effect either vector/mRNA-based vaccine or vector/inactivated vaccine in both humoral and cellular immune response. Notably, the heterologous regimens induced the potential protection against the variant of concern, even to the Delta variant.

Conclusions: The current findings provided evidence about the higher induction of robust immunogenicity and tolerated reactogenicity of heterologous vaccination regimens (vector-based/mRNA vaccine or vector-based/inactivated vaccine). Also, this study supports the application of heterologous regimens against COVID-19 which may provide more opportunities to speed up the global vaccination campaign and maximize the capacity to control the pandemic.

1. Introduction

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in a global pandemic in late 2019 [1]. As of 10th Jan 2022, there have been over 3.0 million confirmed cases of COVID-19, with 5,464,532 deaths reported worldwide [2], prompting unprecedented efforts to contain the virus [1,3,4]. Covid-19 has not only killed more than five million people worldwide but has also left at least 1.5 million orphans, leading to a dramatic burden on the healthcare system and social security [5]. Globally, vaccination programmes have proved to be safe, effective and save lives [6,7]. However, most vaccines do not confer 100% protection potential, and it is not known how the current vaccines will prevent future transmission of SARS-CoV-2 [8], given emerging variants [9]. But vaccination is an effective tool to reach herd immunity and to interrupt the spreading of the disease against current and future variants [9,10]. The SARS-CoV-2 vaccines were developed in different platforms such as inactivated virus, protein subunit, vector-based and mRNA-based vaccines [3]. Heterologous
vaccination refers to the use of booster and priming vaccines developed with different platforms. Heterologous vaccination against COVID-19 should be considered under some circumstances. There are some reasons for using heterologous regimen in clinical practices: (1) intermittent supply shortages of vaccines due to limited capacity in vaccine production and logistic challenge of distributing the right vaccines into the right people at the right time; (2) rare but severe adverse events of vector-based vaccines (e.g., thromboembolism in Oxford-AstraZeneca ChAdOx1-S COVID-19 vaccine); (3) emerging SARS-CoV-2 variants lead to demand for alternative second vaccination. Heterologous vaccine regimens were applied for other diseases including tuberculosis, yellow fever, and influenza [11,12]. Matching two different vaccine platforms could increase efficacy and elicit a strong and long-lasting immune response [13]. Heterologous prime-boost vaccination against SARS-CoV-2 was used in several countries although evidence of safety and robust immunogenicity to support the application of the heterologous regimens was scarce. We conducted this systematic review to investigate and point out the reactogenicity and immunogenicity of heterologous vaccine regimens for preventing COVID-19 disease.

2. Methods

2.1. Eligibility criteria

We included clinical trials and observational studies that examined the reactogenicity and immunogenicity of heterologous regimens of COVID-19 vaccine in healthy adults (uninfected human subjects). We considered published articles in peer-reviewed journals or preprints in English up until September 29, 2021.

3. Search strategy

We searched PubMed, Cochrane Library, Embase, and pre-print servers (Medrxiv and BioRxiv) to identify the relevant studies. Databases were searched with pre-specified keywords including “COVID-19”, “SARS-CoV-2”, “Coronavirus”, “prime-boost”, “vaccine”, “immunization”, “inoculation”, “heterologous”, “mix”, “match”, and “combination”. The complete search strategy is detailed in Supplement file.

3.1. Study selection

After removing exact duplicates, two authors (T.T.N and G.V.V) independently screened the titles and abstracts of the articles to identify the potentially eligible studies. For those selective studies, the two authors independently assessed the full-text articles for eligibility for inclusion in this review. Disagreements between the authors on the inclusion of a given study were resolved by discussion between T.T.N and G.V.V to clarify eligibility. If no consensus was reached, the article was further evaluated by the third author (T.H.T.Q).

3.2. Data extraction and statistical analysis

Following PRISMA guideline, two authors (N.T.T and V.V.G) independently extracted the following data: general study information (authors, year of publication, and location of study), study characteristics, subgroup of study, sample size, description of vaccine, vaccination regimens, reactogenicity, immunology, and information to assess the quality of the study. Because of heterogeneity of quantifications, criteria for positivity vary in different studies, reported outcomes; comparison between trials are impossible for direct meta-analysis. Therefore, we conducted the network meta-analysis using the extracted data for reactogenicity of vaccination.

3.3. Quality assessment

Two reviewers (N.T.T and V.V.G) independently assessed study quality and discussed if disagreements occurred. If no agreement was reached, the study quality was evaluated by an additional reviewer (T.H.T.Q). The Cochrane risk of bias instrument was used to assess the risk of bias for clinical trials. We classified a clinical trial as high risk of bias if at least one category was rated as high risk of bias [14]. The Newcastle-Ottawa quality assessment scale was used to assess the risk of bias for observational studies. We classified observation studies with ≥7 stars as low risk of bias, 5 or 6 stars as medium risk of bias, and less than 5 stars as high risk of bias [15] (Table S1).

4. Results

4.1. Study selection and description

A total of 7288 papers were found based on the search strategy (2341 PubMed, 1604 EMBASE, 96 Cochrane library, 1481 MedRxiv; 1766 BioRxiv). After exclusion of exact duplicates, we screened titles and abstracts of 6333 articles to identify 76 potentially eligible articles. Of 76 articles, 21 articles met eligibility criteria and were included. Of 21 eligible studies, two papers were excluded because one study was third dose study [16] and another did not get the suitable outcome [17]; 19 studies were included in this review with 5 clinical trials and 14 observational studies (Fig. 1). The description of chosen studies was detailed in Table 1 with all the studies are conducted in 2021 year.

4.2. Risk of bias

Of 5 clinical trials, two studies were high risk of bias. One trial did not blind outcome assessment [18] and another trial was lack of random sequence and blindness of participants and personnel [19]. The remaining 3 clinical trials were low of bias although they did not provide sufficient information to evaluate blindness of participants and personnel, blindness of outcome assessment, or selective reporting (Table S2). Of the 14 observational studies, 12 were low risk of bias. The other two studies were medium because of the unrepresentativeness of the exposed cohort and inadequacy of following up [20,21] (Table S1).

Fig. 1. Flowchart of the searching protocol and the final articles for systematic review. There studies were excluded because of third dose study [16], not suitable outcome [17], case report [23,54,55]. These studies did not get the inclusion criteria although the studies conducted in combination of the COVID—19 vaccines.
In Table 1, a summary of included studies on heterologous COVID-19 vaccination is provided. The table presents the author, country, study design, vaccine regimens, time period after boosting, mean age of participants, gender distribution, vaccine regimen, and sample size for each study.

### 4.3. Reactogenicity

Of the nine studies reported the safety of vaccine, the local reactions included injection site pain [18,22,26], redness [18,22,23,26], pruritus [18,22,26], hardness [18,22], swelling [18,23,26], and urticarial [22] were reported. One study conducted in solid organ transplant recipients, and showed the lower incidence of adverse events than healthy controls [18]. Overall, the local adverse events were mild or moderate and showed the lower incidence of adverse events than healthy controls [18,22,23].

In term of systemic reactions, feverishness [18,23–26], fatigue [18,23,24,26], diarrhea [18,23], myalgia [18,22,23,24,26], arthralgia [18,22,23], malaise [18,22,25], chill [18,22,24,27], headache [18,22,23,24,26,27], and nausea [18,22,23,26] were reported. No serious adverse events were reported in studies investigated reactogenicity. Although one study reported serious events in 4 participants, it was not related to the vaccination [28]. The result from network meta-analysis showed that the incidence of fever symptom was higher in the heterologous vaccination of vector-based and mRNA vaccine compared to homogeneous vaccination. In case of vector-based vaccine and inactivated vaccine, the feverishness was the same between two groups (Fig. 2). The pyrexia events were managed by administration of antipyretic medication to reduce symptoms within several days post vaccination [18,25,23]. Table S3 was detailed systemic reactions through the participants.

### 4.4. Immunogenicity

#### 4.4.1. Heterologous regimens of vector-based and mRNA-based vaccine

In general, the immunogenicity induced by heterologous ChAd/BNT
Different immunogenicity was not significantly influenced by age or sex. In contrast to, the T cell response had trend forwards to higher than or equal in heterologous group [23,28,30,32,34,21]. The antibody responses against the variant of concern \(\alpha\), \(\beta\), and \(\gamma\), The antibody responses against the Delta variant in heterologous regimens were higher than homologous regimen [20,24,25]. The greater immune response was reported in combination between vector-based/mRNA vaccine and vector-based/inactivated vaccine [25] (Table 4). These studies reported the evaluation of geometric mean titers of neutralizing antibody against the variants. The spread of new variant also raised a huge concern due to the reduction of vaccine protection or efficacy of drug therapy. Therefore, the superior immunogenicity of heterologous vaccine regimens supported the application of the heterologous regimens in the nationwide vaccine programs.

5. Discussion

The present work evaluated reactogenicity and immunogenicity of SARS-CoV-2 heterologous vaccination regimens in comparison to homologous vaccination regimens to provide scientific evidence in determination of vaccine strategy for the pandemic. In regard to the reactogenicity, the local and systematic reactions were well tolerated and there were no severe events occurring by vaccination. There was vaccination was more potent compared to homologous ChAd/ChAd vaccination in most of studies (Table 2). These findings were similar in both humoral and cellular immune response. Particularly, the anti-spike S antibody response in group vaccinated with heterologous regimens was high [22,24,21,29] and higher than groups vaccinated with homologous regimens [28,30–32]. Only two studies showed that the anti-spike S antibody response in group vaccinated with heterologous regimens was the same as groups vaccinated with homologous regimens [23,33]. Additionally, the receptor-binding domain (RBD) specific antibody was high in two studies [29,22,23]. The neutralizing antibody of group vaccinated with heterologous regimens was high [22,24,29] and higher than groups vaccinated with homologous regimens [23,28,34,33]. Only two studies showed that neutralizing antibody of heterologous group was the same as groups vaccinated with homologous regimens [32,35]. In term of cellular response, the T cell response in group receiving heterologous regimens was high [22,24] [27,35] and higher than group receiving homologous regimen [23,28,30]. Only one study showed the same T cell response between heterologous and homologous regimens [33]. Notably, the B cell response was investigated in one study and showed similar extent in expansion of spike-specific memory B across regimens [30]. While evaluating combination vector-based/mRNA and BNT/BNT vaccination, the immunogenic effect was not consistent across studies. The spike protein Ab level was less than or equal; in contrast to, the T cell response had trend forwards to higher than or equal in heterologous group [23,28,30,32,34,21]. Different immunogenicity was not significantly influenced by age or sex [21,30]. When mRNA vaccine platform derived from different company (Pfizer or Moderna), the immunological activity was consistent in the previous review with the higher immune response being observed in heterologous compared to homologous ChAd/ChAd vaccination (Table 2). These findings supported the mRNA booster vaccination in ChAd prime individuals in order to solve the shortage of vaccine delivery.

4.4.2. Heterologous regimen of vector-based and inactivated vaccine

Because of emergency vaccine program, the heterologous vaccine regimens combined different vaccine platforms in different orders (e.g., vector-based prime/inactivated boost or inactivated prime/vector-based boost). Although the consideration of anxiety, safety, and efficacy was raised, the heterologous vaccine strategies were demonstrated the higher antibody response compared to inactivated prime-boost vaccine. Particularly, the spike protein antibody was higher in heterologous vaccination regimens compared to homologous vaccination regimens when combining different vaccine strategies in different orders (e.g., vector-based prime/inactivated boost or inactivated prime/vector-based boost). These studies reported the higher antibody response compared to inactivated prime-boost vaccine. Particularly, the spike protein antibody was higher in heterologous vaccination group compared to homologous vaccination group of vector-based vaccine [25] or homologous vaccination of inactivated vaccine [36]. The neutralizing antibody response and RBD antibody response were higher in participants vaccinated with heterologous vaccination than participants vaccinated with homologous vaccination [26]. In contrast, the RBD antibody was lower among group vaccinated with heterologous regimen than group vaccinated with homologous regimen of vector-based vaccine [25]. Moreover, the T cell response was reported in covaxin/covaxin and ChAd/ChAd groups with the forward higher response was in ChAd/ChAd vaccination [25] (Table 3). On the other hand, while evaluating the IgG1/IgG4 response of CoVac and Convidecia vaccine, the heterologous group induced more potent response than homologous group [26]. Interestingly, the combination of vector and inactivated virus vaccine could offer potent immune memory in individuals, this might be the effect of immunodominance hierarchy which focusing to the insert in inactivated vaccine group [37,38].
Table 2

Immunogenicity of heterologous regimens including vector-based and mRNA-based vaccines (ChAd/BNT or ChAd/mRNA-1273).

| Vaccine platform | Studies   | Outcomes          | ChAd/BNT (Mean (95% CI)) | ChAd/ChAd (Mean (95% CI)) | BNT/BNT (Mean (95% CI)) | Major results                                                                 |
|------------------|-----------|-------------------|--------------------------|---------------------------|-------------------------|------------------------------------------------------------------------------|
| ChAd and BNT     | Borobia   | Spike protein Ab  | 3684.87 BAU/ml (3851.58–4920.85), Ratio was 36.41-fold increase from baseline | ChAd prime only: 101.2 BAU/ml (82.45–124.22) | NA                      | Heterologous vaccination induced robust response                               |
|                  |           | RBD Ab            | The number was higher compared with ChAd prime: 7756.68 BAU/ml (7371.53–8161.96) | 99.84 BAU/ml (76.93–129.59) |                         |                                                                               |
|                  |           | Neutralizing Ab   | GMT: increased 45-times, from 41.84 to 1905.69 (1625.65–2233.98) | Neutralizing Ab | 41.81 (27.18–64.32) |                                                                               |
|                  |           | T cell response   | IFN-γ significantly increased with GMT: 521.22 pg/ml (422.44–643.09) |   | 122.67 pg/ml (88.55–169.95) |                                                                               |
| Liu [28]         | Serum Ab  | Spike protein Ab  | 12,906 ELU/ml (11,404–14,504) | Serum Ab | 1392 ELU/ml (1188–1360) | 14,080 ELU/ml (12,491–15,871) | The higher immunogenicity of mixing vaccination compared with ChAd/ChAd was demonstrated |
|                  | RBD Ab    | Pseudotype virus neutralizing Ab (NT50): 515 (430–617) | RBD Ab | 61 (50–73) | 574 (475–694) |                                                                               |
|                  | T cell response | SFC per million PBMCs: 184 (152–223) | T cell response | 48 (37–61) | 80 (63–101) |                                                                               |
| Hallup [23]      | Serum Ab  | Spike protein Ab  | 100% (88.6–100) | Serum Ab | 83% (66.4–92.7) | 90% (74.4–96.5) | The heterologous improved immunogenicity compared with homologous ChAd/ChAd |
|                  | RBD Ab    | Pseudotype virus neutralizing Ab (NT50): 515 (430–617) | RBD Ab | 4.9 S/Co (4.3–5.6) | 5.4 S/Co (4.8–5.9) | 99% (94.6–99.5) |                                                                               |
|                  | T cell response | INF-γ concentration: 4762 mIU/ml (IQR: 2723–8403) | T cell response | 1061 mIU/ml (IQR: 599–2274) | 2026 mIU/ml (IQR: 1459–4621) |                                                                               |
| Groj [24]        | Spike protein Ab | Neutralizing Ab | Median IgG titers increased 135-fold (63.9 U/ ml, 4.27–2005–8815 U/ml, 1206–19,046) | Neutralizing Ab | Median ACE2 neutralization increased after BNT booster (62%, 32–95–98%, 89–98) |                                                                               |
|                  |           | T cell response   | 100% participants developed CD4+ T cells and 89% produced CD8+ T cells | T cell response | 80% (63–101) |                                                                               |
| Barros [30]      | Spike protein Ab | Ab IgG: 625.7 RU/mL/Ab IgA: 3.76 RU/ml | Ab IgG: 160.9 RU/mL/Ab IgA: 0.87 RU/ml | Ab IgG: 574.1 RU/mL/Ab IgA: 5.06 RU/ml | Mixing vaccination provided potent higher immune response to ChAd/ChAd group. Boosting with BNT induced higher frequency of T cells response |
|                  |           | T cell response   | A significant higher T cell response in ChAd/ BNT group | T cell response | 97% (88.6–99.7) |                                                                               |
|                  |           | B cell response   | Similar extent in expansion of spike-specific memory B in all groups | B cell response | 90% (83.8–94.7) |                                                                               |
| Behrens [31]     | Spike protein Ab | Spike protein Ab | 611.0 RU/ml (SD: 104.5) | Spike protein Ab | 171.9 RU/ml (SD: 121.8) | Study supported for heterologous boost vaccination of individuals with completed homologous ChAd vaccination |
|                  |           | T cell response   | 88% (71.9–96.5) | T cell response | 84% (71.9–96.5) | Heterologous induced strong and broad humoral response |
|                  |           | B cell response   | 96% (88.6–100) | B cell response | 96% (88.6–100) | Heterologous induced strong and broad humoral response |
| ChAd, mRNA, BNT  | Fabriicus | Neutralizing Ab   | ChAd/mRNA: (> 85% participants exhibited stronger neutralizing capacity | mRNA/mRNA | ChAd/ChAd: (> 90% vaccinated individuals exhibited no or medium level neutralization capacity | Heterologous vaccination booster regimens with mRNA could allow enhanced protection against SARS-CoV-2 |
|                  |           | T cell response   | Peak IFN-γ secretion was significant stronger | T cell response | 100% (96.5–99.5) |                                                                               |
|                  | Normark   | Spike protein Ab  | 115 time as high as, 128,108 | Spike protein Ab | 1224 | Potent induction of SARS-CoV-2 immune response had trend to be higher in heterologous group |
|                  |           | RBD Ab            | 125 times as high as, 41,680 | RBD Ab | 1224 |                                                                               |

(continued on next page)
Inconsistent between the total results of adverse reactions as equal reactions [22,23], higher reactions [18,32,25,26] in mixing vaccination group. The explanation for more frequency of systemic reactogenicity in heterologous groups might be the higher reactions in young age group with ChAd and BNT [39,40] or the variety in interval of prime-boost vaccination time [41]. In contrast, after the second dose vaccination, the adverse events in individuals immunized with the vector-based vaccine was more frequent compared to mRNA vaccines [42]. The systemic events were generally less frequent in individuals receiving heterologous regimen than individuals receiving homologous regimen [27, 43]. However, in solid transplant recipients, the systemic events in individuals receiving heterologous regimen was more frequent than in individuals receiving homologous regimen. In term of heterologous regimen of vector-based vaccine and inactivated vaccine, the similar document was cited of the slightly higher incidences of injection-site and systemic reactions. One study reported differences between male and female in reactogenicity because of stronger immune response among females than males [44]. The remaining studies did not observe the difference in subgroup analysis.

Immunological data suggested that either heterologous regimens of vector-based/mRNA or vector-based/ inactivated vaccine might be highly effective in preventing COVID-19. These findings were observed in the study conducted on animal [45]. The mechanism for this action could be that using different platforms has induced protection from different pathways. The mRNA vaccine elicited extremely high neutralizing and binding antibody titers while the vector-based vaccine could be that using different platforms has induced protection from similar pathways. The mRNA vaccine elicited extremely high neutralizing and binding antibody titers while the vector-based vaccine could be that using different platforms has induced protection from similar pathways.
Table 4
Immunogenicity in different variants of concern in reported studies.

| Study | Type of vaccine | Outcomes | Type of variant |
|-------|-----------------|----------|----------------|
| Hillus[23] | ChAd/BNT | The Geometric mean of 50% inhibitory dose (95% CI) | α (B.1.1.7) 956.6 (835.6–1095) |
| | | | β (B.1.351) 417.1 (349.3–498.2) |
| | | | γ (B.1.1.28.1) NA |
| | | | δ (B.1.617.2) NA |
| Behrens[31] | ChAd/ChAd | Neutralization capacity of Ab | Increased in some individuals |
| | | | No effect |
| Hammerichmidt[20] | ChAd/BNT with ChAd | Surrogate virus neutralization tests | ChAd/BNT induced higher levels against all type of variants compared to ChAd/ChAd group. NT90 ≥ 100 in 85% of vaccines in delta variant |
| Fabricius[35] | ChAd/mRNA | Mean neutralization capacity individuals | 87% |
| | | | 76% |
| | | | 48% |
| Normark[29] | ChAd/mRNA | Neutralizing Ab | 85% |
| | | | 73% |
| | | | 56% |
| | | | 15% |
| Kant[25] | ChAd/covaxin | Geometric mean titers with 95% confidence interval (CI) | 151 (80.21–284.3) |
| | | | 48.43 (19.71–119) |
| | | | 52.09 (34.9–77.73) |
| | | | 5.43 (27.26–108.4) |

NA: Not available; CI: confidence interval

inactivated/recombinant subunit/mRNA vaccine vaccination increased levels of neutralizing antibodies and promoted the modulation of antibody responses [51].

With emerging variants of concern, current evidence indicated that the higher immune response in heterologous regimens compared to homogenous regimens against the current type of variants (α, β, γ, δ). The efficacy of heterologous regimens against variants was observed in both humoral and cellular immune response and thus was suggested as a suitable strategy to contain emerging SAR-CoV-2 variants [52]. Besides that, some studies have been conducted to evaluate the third dose application, the result were consistent about the robust immunogenic effect in heterologous vaccination [16,26].

In contrast to the previous articles, we conducted a systematic study has been updated the status of heterologous strategy for not only prime vector/ boost mRNA vaccination but also the prime/boost vector/ inactivated vaccination [41,53]. Moreover, this is the first time the studies about matching vaccine was assessed by powerful tools for systematic study as Risk of bias 2 from Cochrane assessment for clinical trials and NewCastle- Ottawa assessment scales for cohort studies. We also used more source of data from printed and preprinted papers to entirely evaluated the matching vaccination. Additionally, the consideration for immunogenicity against the variants have been pointed out as the evidence for potent immune response of mixing vaccination. Thus, this systematic review was essential, important to give comprehensive, completed evaluation of heterologous vaccine strategy. Because of the variety of outcome quantified numbers, the network meta-analysis used the same outcome of previous review, however the method to calculate was different and this result was more intuitive to evaluate the reactogenicity. Besides that, the local and systemic reactions were assessed and pointed out to demonstrate the effect of heterologous or homogenous vaccination to the participants in studies (Table S3, S4).

The present study has several strengths. This review followed the PRISMA construction for conducting the assessment. Although the direct meta-analysis was impossible, the network meta-analysis was carried out to evaluate the reactogenicity of heterologous vaccination in term of fever symptoms which frequently occurred by COVID-19 vaccines. The risk of bias was assessed separately for clinical trials and observational studies by using Cochrane assessment and NewCastle- Ottawa assessment scales.

This systematic review was subjected some limitations. We cannot compare directly between studies because of the diversity of quantitative methods for antibody responses. Therefore, the work has lack of direct meta-analysis result. The interval of prime-boost injections varied between studies and has been not pointed out because of complication and the supplier contradiction.

6. Conclusion

The systematic review provided assessment and evidence about the higher induction of robust immunogenicity and tolerated reactogenicity of heterologous regimens (vector-based/mRNA vaccine or vector-based/ inactivated vaccine). The heterologous vaccination regimens might be an effective tool to contain the COVID-19 pandemic and the emergence of new variants. A future studies should investigate the efficacy and effectiveness of heterologous vaccination regimens.

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Declaration of conflicting interests

The authors declare no conflict of interest.

Data availability

The datasets used for the analysis in the present study are available from the corresponding author on reasonable request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopharma.2022.112650.

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