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Previous exposure to Spike-providing parental strains confers neutralizing immunity to XBB lineage and other SARS-CoV-2 recombinants in the context of vaccination

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ABSTRACT

The emergence of SARS-CoV-2 recombinants is of particular concern as they can result in a sudden increase in immune evasion due to antigenic shift. Recent recombinants XBB and XBB.1.5 have higher transmissibility than previous recombinants such as "Deltacron." We hypothesized that immunity to a SARS-CoV-2 recombinant depends on prior exposure to its parental strains. To test this hypothesis, we examined whether Delta or Omicron (BA.1 or BA.2) immunity conferred through infection, vaccination, or breakthrough infection could neutralize Deltacron and XBB/XBB.1.5 recombinants. We found that Delta, BA.1, or BA.2 breakthrough infections provided better immune protection against Deltacron and its parental strains than did the vaccine booster. None of the sera were effective at neutralizing the XBB lineage or its parent BA.2.75.2, except for the sera from the BA.2 breakthrough group. These results support our hypothesis. In turn, our findings underscore the importance of multivalent vaccines that correspond to the antigenic profile of circulating variants of concern and of variant-specific diagnostics that may guide public health and individual decisions in response to emerging SARS-CoV-2 recombinants.

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KEYWORDS SARS-CoV-2; recombinants; humoral immunity; neutralization; vaccine

Introduction

SARS-CoV-2 recombinants emerging during the surges of COVID-19 have raised significant concerns, primarily due to their potential to accelerate immune evasion due to antigenic shift. Among these recombinants, the newly identified XBB lineage has garnered considerable attention. It came into existence through the recombination of two highly diversified lineages, BJ.1 and BA.2.75.2, both derivatives of the Omicron BA.2 lineage. Remarkably, the XBB variants swiftly spread across populations worldwide, including those who had been vaccinated and those with hybrid immunity.

In contrast, a variant known as "Deltacron", which originated in early 2022 from the recombination of Delta and Omicron BA.1 lineages, exhibited limited spread compared to XBB. We postulate that this difference in transmission dynamics reflects the varying levels of pre-existing immunity within the population. Specifically, individuals had developed some degree of immunity against the parental strains of Deltacron, either through vaccination or prior infection. However, due to antigenic shift in newly emerging variants, this immunity was substantially less effective against the parental strains of XBB.

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To test our hypothesis, we reconstructed naturally occurring XBB and Deltacron recombinants, and conducted comprehensive assessments of their neutralization by serum samples collected from individuals encompassing a wide range of immune statuses, including those who had recovered from infection, individuals who had been vaccinated, and those with hybrid immunity. This investigation aimed to shed light on the interplay between recombinant variants and the existing immune landscape, and to offer insights for effective vaccine design.

Methods and materials

Human serum samples

Human serum samples were obtained from three sources:

i The Curative clinical trial provided 52 samples. This trial aimed to investigate immune evasion by the SARS-CoV-2 virus, approved under Advarra's Pro00054108, part of the University of California, Los Angeles Protocol Record PTL-2021-0007, and registered under ClinicalTrials.gov Identifier NCT05171803.
ii We acquired 25 remnant plasma samples from hospitalized COVID-19 patients at UCSF through UCSF Clinical Laboratories. These samples were stored in a biobank. A retrospective review of medical records collected relevant demographic and clinical metadata. This process followed approved "no subject contact" protocols by the UCSF Institutional Review Board (protocol number 10-01116).
iii An additional 10 plasma samples were procured through the UMPIRE study (UCSF Employee and Community Member Immune Response), identified by protocol number 20-33083. This study focused on collecting whole blood and plasma samples, assessing immune responses to vaccinations (including booster shots) and vaccine breakthrough infections. Consent was obtained from UMPIRE participants at the UCSF CTSI Clinical Research Service (CRS) Laboratory, where nurses and phlebotomists collected their blood.

Blood samples underwent standard venipuncture, allowing for the extraction of up to 15 ml of whole blood. The collected blood was left to coagulate at room temperature for 30–60 min, followed by centrifugation at 2200–2500 rpm for 15 min at room temperature. Resulting serum samples were stored on ice until transportation to the laboratory, where they were divided into aliquots and stored at −80°C for future use. It's important to note that all patients in the eight study groups tested negative by PCR at the time of serum collection.

These trials included diverse adult participants with varying immune backgrounds, including those who had previously received COVID-19 vaccinations or had a history of prior COVID-19 infection. In total, our study cohort comprised 87 individuals, categorized into eight groups: (i) Two vaccine doses (n = 10), (ii) Three vaccine doses (n = 10), (iii) Unvaccinated individuals infected with BA.1 (n = 8), (iv) Unvaccinated individuals infected with BA.2 (n = 9), (v) Unvaccinated individuals infected with B.1.617.2 (n = 11), (vi) Vaccinated individuals experiencing BA.1 breakthrough (n = 11), (vii) Vaccinated individuals experiencing BA.2 breakthrough (n = 23), (viii) Vaccinated individuals experiencing Delta breakthrough (n = 5). It's important to note that individuals in the breakthrough population had received either two or three doses of mRNA vaccine.

Infectious clone preparation

Infectious clones for Deltacron (Figure S1), XBB, XBB1.5 (Figure S2) and BA.2.75.2 variants were prepared using a recently reported viral genome assembly and rescue strategy [1]. The virus infection experiments were performed in a Biosafety Level 3 laboratory. Working stocks of SARS-CoV-2 variants were made in Vero-ACE2-TMPRSS2 cells and were stored at −80°C until used.

Virus neutralization assay

The serum samples were heat-inactivated at 56 °C for 30 mins. The sera were diluted 1:35, 1:175, 1:525, 1:1575, 1:4725, 1:14,175 in 50 µL serum-free DMEM. Each dilution was combined with 50 PFU (50 µL) of SARS-CoV-2 recombinants or parental strains. The mixture was mixed gently and incubated at 37°C for 30 mins, before assessment of virus neutralization through the plaque assay.

Plaque assay

Vero-ACE2-TMPRSS2 cells (gifted from A. Creanga and B. Graham at NIH) grown to monolayers were infected with the mixtures of serum dilutions and virus. After one hour, the cultures were overlaid with 2.5% Avicel (Dupont, RC-591) and infections allowed to proceed for 72 h. The cells were then fixed with 10% formalin for one hour and the plaques were visualized by crystal violet. The plaques were counted for each serum dilution and the neutralization titre at 50% (NT50) was determined as the dilution factor leading to the neutralization of 50% of the virus.

Results

Selection of SARS-CoV-2 recombinants and immune population

Although many SARS-CoV-2 Deltacron and other recombinants exist [2], we focused on Spike Deltacron recombinants because Spike is the main target of neutralizing antibodies after infection and is the only target of mRNA vaccines. We used reverse genetics to create two recombinant Deltacron variants that had been previously identified or documented in sequencing databases [3–6]: one where the Delta variant carries the Spike sequence from Omicron-BA.1 (δ/o-Spike) and the other where the Omicron-BA.1 variant harbours the Spike sequence from Delta (o/δ-Spike) (Figure S1) [1]. Each recombinant also included mutations (inside or outside Spike) found in > 90% of GISAID sequences of circulating Deltacron variants as of January 2022. Our XBB infectious clone harbours a combination of BJ.1 and BA.2.75.2 mutations found in > 90% of GISAID XBB sequences as of October 2022 (Figure S2). The recombination point is within the Spike receptor binding domain protein, and the N-terminal 459 amino acids are from BJ.1 and the C-terminal 814 amino acids from BA.2.75.2. The XBB.1.5 infectious clone had few different mutations across the genome and were contained in >90% of GISAID sequences as of December 2022 (Figure S2).

We evaluated sera from a cohort of 87 individuals that fell into eight groups: vaccinated people who received (a) two vaccine doses or (b) three vaccine doses; unvaccinated individuals infected with (c) BA.1, (d) BA.2, or (e) Delta; and vaccinated individuals with (f) BA.1 breakthrough, (g) BA.2 breakthrough, or (h) Delta breakthrough. Individuals in the breakthrough population had received either two or three doses of the mRNA vaccines. The clinical characteristics of the cohort are provided in Table S1 in the supplementary appendix. For 27 (40%) of the 67 infected individuals, the presence of Omicron or Delta had been confirmed by sequencing the nasopharyngeal/nasal swabs; for the 40 other infected individuals, the infectious strain is inferred based on the date of sample collection. We tested all sera for their ability to neutralize Deltacron XBB, XBB.1.5 recombinants, and their parental strains (Delta, BA.1 and BA.2.75.2) using whole-virus neutralization assay. Results are expressed as neutralization titres at 50% value (NT50), which represents the serum titres that neutralizes 50% of the virus in our assay (Figure 1) [7]. In this system, the greater the NT50, the stronger the neutralizing capacity of the serum.

Vaccination enhances neutralization of Deltacron but not of the XBB lineage

We first compared the neutralization titres of the vaccinated (group a, two vaccine doses) and boosted populations (group b, three vaccine doses). The sera of boosted individuals exhibited 32-fold and 15-fold higher neutralization of o/δ-Spike and δ/o-Spike, respectively, than did the sera of non-boosted vaccinated individuals (Figure 1(A and B)). These findings suggest that an additional dose of mRNA vaccine provides substantial protection against Deltacron recombinants, similar to its effect against other SARS-CoV-2 variants [8,9]. However, δ/o-Spike was less susceptible than o/δ-Spike to neutralization by sera from vaccinated or boosted individuals (by a factor of 3.3 and 4.2, respectively; Figure 1(A and B)), indicating partial immune evasion by the Omicron Spike protein [7,10,11]. Similar to their parental strain BA.2.75.2, XBB and XBB.1.5 completely escaped neutralization by sera from both the vaccinated (NT50 5.2-6) and boosted (NT50 16–22) individuals (Figure 1(C–E)). The findings are consistent with the expectation that vaccinated sera lose their potency against Spike sequences of newly emerging variants [12,13].

Sera from Omicron or Delta convalescents neutralize Deltacron better than XBB recombinants

Next, we examined unvaccinated individuals recovering from Delta, BA.1 or BA.2 infections (groups c-e). Those recovering from a Delta infection showed a 59-fold higher NT50 against the o/δ-Spike than the δ/o-Spike recombinant (2845 vs. 48, $p = 0.008$) (Figure 1(A and B)). These results align with neutralization of the parental strains, where sera from Delta convalescent individuals had a 42-fold higher NT50 against Delta than BA.1 (NT50 against Delta: 2117, against BA.1: 50, $p = 0.01$) (Figure S3(A and B)) [7]. Reciprocally, sera from BA.1 convalescent individuals showed higher titres against the δ/o-Spike than o/δ-Spike recombinant (NT50 314 vs. 162) (Figure 1(A and B)). The BA.1 convalescents' sera also neutralized the parental BA.1 strain 5.2-fold better than the δ/o-Spike recombinant (NT50 1636 vs. 314, $p = 0.02$) (Figure S3(A and B)) [7], indicating that infection with BA.1 generates neutralizing antibodies against non-Spike proteins in addition to the Spike of BA.1. Interestingly, sera from BA.2 convalescent individuals showed the least neutralization of both Deltacron recombinants, even δ/o-Spike (NT50 < 100), XBB (NT50 5) and of XBB.1.5 (NT50 21), indicating that in unvaccinated individuals, BA.2 infection triggers a less robust humoral response than BA.1 does, which in turn underscores antigenic disparities between the Spike proteins of these variants (Figure 1(A–D)). None of the convalescent sera were able to efficiently neutralize XBB or XBB.1.5 (NT50 < 20) (Figure 1(C–E)). The observations are consistent with the model that exposure to the Spike-providing parental strain is critical for efficient neutralizing immunity.

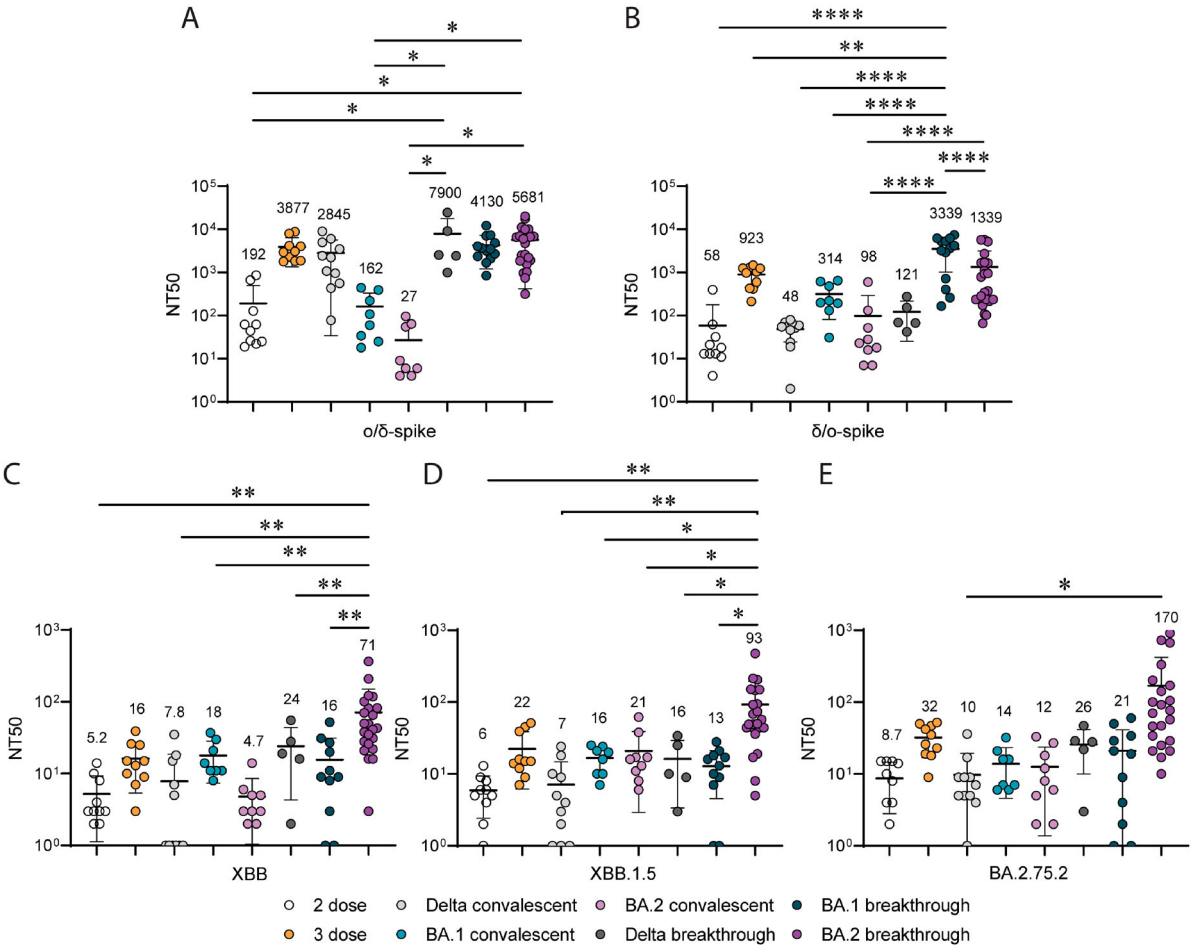

Figure 1. Vaccine-induced and hybrid immunity effectively neutralizes Deltacron variants but not XBB lineage. (A–E). Scatter dot plots of neutralizing-antibody titres against Omicron-Delta spike (o/δ-spike), Delta-Omicron spike (δ/o-spike), XBB, XBB.1.5 and BA.2.75.2 variants by sera from: two-doses mRNA-vaccinated individuals ($n = 10$); vaccinated and boosted (three doses of mRNA vaccine) individuals ($n = 10$); unvaccinated individuals infected with Delta ($n = 11$), BA.1($n = 8$); BA.2 ($n = 9$); vaccinated or boosted individuals with breakthrough infections by Delta ($n = 5$), BA.1 ($n = 11$), and (H) BA.2 ($n = 23$). In all cases, geometric mean values for the 50% neutralization titres (NT50) are provided at the top of the plots. Each dot represents an individual serum sample. Statistical significance was analyzed by unpaired ordinary one-way ANOVA with Tukey's multiple comparison test (*$P < 0.05$, **$p < 0.001$,**** $p < 0.0001$). The details regarding samples (group, age, sex, COVID-19 infection status, severity, vaccination dates, and sample collection dates after infection or symptoms are summarized in supplementary data Table 1).

Hybrid immunity conferred by BA.2 infection in vaccinated individuals induces partial protection against XBB lineage

Finally, we examined the vaccinated individuals recovering from breakthrough infections with Delta, BA.1 or BA.2 (groups f–h). The sera from Delta breakthrough individuals displayed the highest NT50 recorded across all our experiments, an NT50 of 7900 against the o/δ-Spike variant. This NT50 was 2.7-fold that of Delta convalescents without vaccination (2845) and 2 fold that of boosted individuals (3877), illustrating the superiority of hybrid immunity against Delta Spike relative to vaccination or Delta infection alone (Figure 1(A)). This NT50 was also 65-fold higher ($p = 0.001$) than the NT50 of the same sera against the δ/o-Spike recombinant indicating immune evasion by BA.1 spike (Figure 1(A and B)).

Individuals with BA.1 or BA.2 breakthrough infection neutralized both the δ/o-Spike and the o/δ-Spike variants with fairly high NT50s (ranging from 1339 to 5381) relative to the NT50 of unvaccinated BA.1- or BA.2-infected individuals (ranging from 27 to 314) (Figure 1(A and B)), suggesting that immune recall by breakthrough Omicron infections (BA.1 or BA.2) confers substantially higher and broader protection against Deltacron recombinants than do Omicron infections in the unvaccinated population. Interestingly, the sera from the BA.2 breakthrough group showed the most potent neutralization of XBB (NT50 71) and XBB.1.5 variants (NT50 93) among all sera (Figure 1(C and D)), even though this protection was limited. In particular, it neutralized the XBB lineage 3–7-fold more efficiently than did sera from the Delta ($p = 0.003$) and BA.1 ($p < 0.0001$) breakthrough groups. The results indicate the major antigenic shift of the XBB lineage, which stems from BA.2. In addition to SARS-CoV-2 recombinants. we also evaluated all study groups for their ability to neutralize BA.2.75.2, one of the parental strains of XBB.

As expected, BA.2 breakthrough sera was the most potent, with an NT50 of 170, 6.5- and 8-fold higher than the NT50 of the Delta and BA.1 breakthrough sera, respectively (Figure 1(E)).

This highlights the significance of tailored vaccine strategies based on currently circulating variants and utilizing diagnostics that are specific to these variants as a response to the evolving SARS-CoV-2 recombinants, especially since future recombinant strains are expected to stem from the currently circulating ones.

Discussion

Our study set out to explore whether the differential spread of SARS-CoV-2 recombinants, particularly the constrained propagation of Deltacron recombinants compared to the broad distribution of the XBB lineage, reflected pre-existing immunity to specific SARS-CoV-2 variants. To investigate this hypothesis, we generated XBB, XBB.1.5 and Deltacron (o/δ-Spike and δ/o-Spike) strains similar to those occurring naturally and evaluated their neutralization by sera from individuals with a diverse range of immune statuses, encompassing individuals who have recovered from infection, those who have been vaccinated, and those who possess hybrid immunity.

We found that the boosted individuals neutralized one of the Deltacron recombinants (o/δ-Spike) and its parental strain Delta much more efficiently than non-boosted vaccinated individuals did. However, the other Deltacron recombinant (δ/o-Spike) and BA.1 showed partial immune evasion, while the XBB and XBB1.5 recombinants, along with their parental strain BA.2.75.2, showed complete immune escape in vaccine-boosted individuals. These results align with the anticipated decrease in the effectiveness of vaccination and boosting as newly emerging variants diverge from the original Spike sequence [12,13]. Infection by Delta, BA.1 or BA.2 in unvaccinated individuals led to varying neutralization patterns against Deltacron recombinants, highlighting antigenic disparities between these variants. While these sera neutralized the parental Delta and BA.1 strains, the sera from individuals recovering from BA.2 infection had the weakest neutralization activity, suggesting that BA.2 infection induces a weaker humoral response than other strains in unvaccinated individuals. This may indicate significant differences in the antigenic repertoire of the Spike proteins from BA.1 vs. BA.2 variants. Both BA.1 and BA.2 Omicron variants emerged in South Africa around the same time. However, BA.2 distinguishes itself from BA.1 by containing 21 common mutations and 10 unique ones in its Spike protein [14]. Consistent with our findings, previous studies have demonstrated that despite sharing numerous mutations in the Spike protein, Omicron BA.1 and Omicron BA.2 exhibit differences significant enough to impede effective cross-neutralization [15,16]. These observations are consistent with the model that exposure to the Spike-providing parental strain is critical for efficient neutralizing immunity.

Sera from vaccinated individuals recovering from Delta breakthrough infections displayed strong neutralization of the o/δ-Spike variant, showing the superiority of hybrid immunity over immunity conferred by vaccination or Delta infection alone. Nevertheless, due to antigenic disparities in the BA.1 spike, the neutralization capacity of sera from Delta breakthrough cases was significantly lower against the δ/o-Spike recombinant. People with BA.1 or BA.2 breakthrough infections exhibited a robust neutralization against both δ/o-Spike and o/δ-Spike variants that surpassed that seen in convalescent individuals, consistent again with the superiority of hybrid immunity over infection alone. None of the hybrid immune sample showed much efficacy against XBB lineage or its parental strain BA.2.75.2. The best neutralization of the XBB lineage was seen in the BA.2 breakthrough group, although it remained limited (NT50 71-93). Notably, the mean NT50 values of all groups except the BA.2 breakthrough group are similar. This similarity could be attributed to the major antigenic shift of the XBB lineage, which derives from BA.2 and is characterized by 22 unique mutations including 20 amino acid substitutions and 2 deletions compared to the BA.1 variant. The findings suggest that BA.2 is too distant from other strains for cross-neutralization, in the context of hybrid immunization and/or immune recall. These findings support the model of a major antigenic shift in emerging variants, stemming from BA.2 (Figure 1(C–E)), and imply that the BA.2 Spike protein could be an effective immunogen to induce neutralization of XBB lineage by vaccination.

Our study has several limitations. First, the disease severity index of the Delta and BA.1 convalescents in our study was relatively higher than that of the BA.2 convalescent or breakthrough groups, who had suffered relatively mild disease. This difference in disease severity is inherent to the pathogenicities of the variants. Second, the median age of our cohort ranges from 31 to 65 years; thus the results might not be generalizable to people outside this age range. Third, we have a slight overrepresentation of female participants, who often suffer less severe disease than their male counterparts do [17,18].

In spite of these limitations, our findings suggest that vaccination, particularly when boosted, and the hybrid immunity resulting from Delta, BA.1, or BA.2 breakthrough infections, provide effective protection against Deltacron recombinants. This aligns with our hypothesis that the proliferation of Deltacron variants was constrained by pre-existing immunity at that time. In contrast, only hybrid immunity from a BA.2 breakthrough infection could neutralize the

XBB lineage and its precursor strain, BA.2.75.2, albeit to a modest extent (NT50 values of 71 against XBB, 93 against XBB.1.5, and 170 against BA.2.75.2). This modest neutralization, combined with an increased binding affinity of the Spike protein for human ACE2 [19], might facilitate the wide spread of new XBB recombinants within the community. In line with our hypothesis, recent reports have shown that the Spike protein specific to XBB.1.5 elicits broadly neutralizing immune responses against newly emerging XBB variants, including XBB.1.16, XBB.1.9.1, and EG.5 [20,21]. Our data emphasize the benefits of vaccines tailored to encompass the antigenic profiles of prevailing variants of concern and underscore the significance of variant-specific diagnostics. Such diagnostics have the potential to inform decisions in both public health and individual settings when confronted with the emergence of new SARS-CoV-2 recombinants.

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Author contributions

R.K.S., T.Y.T. and M.O. conceptualized the study. R.K.S., T.Y.T, M.M.M, I.S., A.M.S., I.P.C., M.M., T.T., M.M.K., B.S., and G.R.K. performed the investigation. I.S., P.S., K.F., A.S.G., V.S., A.G., J.N., N.K., T.A., A.B., V.H., M.S., L.L., M.B., F.T., Y.W., S.G., G.D., D.R., L.S. and C.Y.C. performed the anti-sera collections. M.M maintained the BSL3 facility. J.A.D., L.S., C.Y.C. and M.O. supervised the study. R.K.S., and M.O. wrote the original draft of the manuscript. R.K.S., T.Y.T., L.S., C.Y.C. and M.O. reviewed and edited the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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