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ORIGINAL ARTICLE

Serological responses and clinical outcomes following a three-dose primary COVID-19 vaccine schedule in kidney transplant recipients and people on dialysis

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Abstract

Objectives. Despite vaccination strategies, people with chronic kidney disease, particularly kidney transplant recipients (KTRs), remained at high risk of poor COVID-19 outcomes. We assessed serological responses to the three-dose COVID-19 vaccine schedule in KTRs and people on dialysis, as well as seroresponse predictors and the relationship between responses and breakthrough infection. **Methods.** Plasma from 30 KTRs and 17 people receiving dialysis was tested for anti-Spike receptor binding domain (RBD) IgG and neutralising antibodies (NAb) to the ancestral and Omicron BA.2 variant after Doses 2 and 3 of vaccination. **Results.** After three doses, KTRs achieved lower anti-Spike RBD IgG levels ($P < 0.001$) and NAb titres than people receiving dialysis ($P = 0.002$). Seropositive cross-reactive Omicron neutralisation levels were achieved in 11/27 (40.7%) KTRs and 11/14 (78.6%) dialysis recipients. ChAdOx1/viral-vector vaccine type, higher mycophenolate dose (> 1 g per day) and lower absolute B-cell counts predicted poor serological responses in KTRs. ChAdOx-1 vaccine type and higher monocyte counts were negative predictors in dialysis recipients. Among ancestral NAb seroresponders, higher NAb levels positively correlated with higher Omicron neutralisation ($R = 0.9$, $P < 0.001$). More KTRs contracted SARS-CoV-2 infection (14/30; 47%) than dialysis recipients (5/17; 29%) and had more severe disease. Those with breakthrough infections had significantly lower median interdose incremental change in anti-Spike RBD IgG and ancestral NAb titres. **Conclusion.** Serological responses to COVID-19 vaccines in KTRs lag behind their dialysis counterparts. KTRs remained at high

risk of breakthrough infection after their primary vaccination schedule underlining their need for booster doses, strict infection prevention measures and close surveillance.

Keywords: antibody response, COVID-19 vaccine, dialysis, immune response, kidney transplant, SARS-CoV-2

INTRODUCTION

Despite advancements in strategies for the prevention and treatment of COVID-19, people with chronic kidney disease (CKD), particularly kidney transplant recipients (KTRs), continue to face a greater risk of developing severe SARS-CoV-2 infection and death.[1,2] Owing to uraemia, immunosuppressants (IS) and complex comorbidities, patients with CKD have blunted and shorter-lived convalescent and vaccine-induced serological immune responses.[1,3–7] Whilst significant strides have been taken to improve outcomes from COVID-19, SARS-CoV-2 is unlikely to be eradicated in the near future, and the emergence of variants of concern (VOC), coupled with waning immunity, continues to place the CKD population at risk. Despite impaired vaccine responses, vaccination is reported to largely protect against severe disease and death in the CKD population.[8,9]

Vaccine development and dosing strategies need to keep pace with the ever-changing landscape of SARS-CoV-2 infection and transmission because of the rapid emergence of VOC. Of all variants described to date, Omicron is thought to be the most divergent VOC.[10] Over 80% of the COVID-19-related deaths in Australia occurred during the first Omicron wave in 2022.[11] The present literature on vaccine responses and SARS-CoV-2 infection outcomes in the CKD population, in particular, transplant recipients is complicated and unfolding.[7,12–14] Whilst it is evident that those on dialysis produce greater vaccine-induced immune responses than transplant recipients, there is mixed evidence on the strength and longevity of their responses. Some studies demonstrated attenuated responses whilst others showed comparable responses to healthy controls.[7,12–14]

Neutralising antibodies (NAb) are widely adopted as a correlate of immune protection.[15] NAb predominantly target the receptor-binding domain (RBD) of the SARS-CoV-2 spike and have been used to model vaccine effectiveness and to inform vaccination strategies including the timing of booster doses.[15,16] However, vaccine immunogenicity studies are heterogenous, adopting different immune assays and positive cut-offs, making comparisons challenging. In addition, there is currently no clear consensus on serological values that confer protection against severe COVID-19 disease.

International vaccination schedules vary owing to geographic, social, political and economic factors impacting vaccine availability. The Australian COVID-19 national vaccine campaign commenced on 22 February 2021, and most people with CKD, including transplant recipients, were only eligible from 22 March 2021.[17] The ChAdOx1 (Oxford/AstraZeneca) and BNT162b2 (Pfizer) vaccines were initially approved by the Australian regulator, the Therapeutic Goods Administration (TGA) for distribution in Australia. Because of vaccine availability, ChAdOx1 was initially the most widely distributed vaccine. Following the reports of thrombosis with thrombocytopenia, a rare but concerning adverse event linked to ChAdOx1 vaccines, the Australian Technical Advisory Group on Immunisation (ATAGI) recommended the use of mRNA vaccines as the preferred vaccine for all under 50 years of age in April 2021 and subsequently for all under 60 years of age in June of 2021.[17] Consequently, the use of mRNA vaccines superseded that of ChAdOx1 with the latter being discontinued in March 2023.[17] Following the development and spread of Omicron subvariants, two bivalent mRNA vaccines containing mRNA encoding for the BA.1 and BA.4.5 omicron sublineage spike proteins were approved for use by ATAGI.[18]

Large variations in vaccine schedule efficacies (50–95%) have been reported in the general population.[19] Predictors of a poor seroresponse to the COVID-19 vaccines include older age, poor renal function and the use of immunosuppressive (IS) medication, particularly the type (i.e. mycophenolate/mycophenolic acid [MMF/MPA], dose [cumulative MMF daily dose $>$ 1.5 g]), and number.[7,20] Advancements in the

understanding of poor vaccine-induced immunogenicity and limited longevity of antibody responses had prompted the recommendation of a third primary dose and multiple booster doses from October 2021.[21,22] Vaccine type as well as homologous versus heterologous vaccination regimen have been shown to affect vaccine-induced immunogenicity.[23–25] The population data analysis in the UK showed that the ChAdOx1 (viral vector) vaccine was particularly less effective against the Omicron variant, with vaccine effectiveness disappearing at 20 weeks following two doses.[23] Similarly, Banki *et al*. (2022) showed that an all-ChAdOx1-based schedule resulted in the lowest neutralising antibody response in the general population compared with an all-BNT161b2 or mixed ChAdOx1/BNT161b2 schedule.[25] Several studies suggest a stronger immune response following a heterologous vaccine schedule.[24,25] Subsequently, international transplant and dialysis organisations had strongly recommended the use of mRNA vaccines (homologous or heterologous schedules) in preference to viral vector vaccines in those with CKD or solid organ transplant.[21,22]

Our primary aims were to quantify the COVID-19 vaccine-induced serological immune responses in patients receiving dialysis and KTRs and to determine the association between these responses and subsequent breakthrough infection risk. We examined the anti-Spike RBD IgG levels and neutralising antibody (ancestral and Omicron) titres, and positive serological response rates in the dialysis and kidney transplant groups. Our secondary aims were to compare serological responses according to vaccine type; to identify the predictors of serological responses to the COVID-19 vaccines in KTRs; and to assess the risk of transplant rejection following vaccination and/or SARS-CoV-2 infection.

RESULTS

Participant demographics and clinical details

Forty-seven participants, 30 KTRs and 17 people receiving dialysis agreed to participate in the study. Plasma from all participants following Dose 2 and for 41 participants (27 transplant and 14 dialysis) following Dose 3 was available for analysis. The transplant group participants were receiving immunosuppressive medications and were older than the dialysis group (Table 1). The median ages were 62 years (IQR 57–65) and 55 years (IQR 46–61) in the transplant and dialysis groups, respectively. Most transplant recipients were receiving mycophenolate (29/30, 97%), tacrolimus (28/30, 93%) and prednisolone (26/30, 87%).

Table 1. Baseline demographics of transplant and dialysis groups at study commencement

	Transplant $n = 30$	Dialysis $n = 17$	P
Age (years)	62 (57–65)	55 (46–61)	0.01
Sex			
Female	10 (33%)	4 (24%)	0.48
Primary disease			
Diabetes	10 (33%)	5 (29%)	0.80
Glomerulonephritis	10 (33%)	8 (47%)	
Hypertension	2 (7%)	1 (6%)	
Other	8 (27%)	3 (18%)	
Transplant duration group			
0–5 years	14 (47%)	N/A	
6–10 years	10 (33%)		
> 11 years	6 (20%)		
Immunosuppression			
Tacrolimus	28 (93%)	0	N/A
Mycophenolate	29 (97%)	0	
1500 mg daily	15 (52%)		
≤ 1000 mg daily	14 (48%)		
Prednisolone	26 (87%)	1 (6%)	
mTORi	2 (7%)	0	
Azathioprine	1 (3%)	0	
eGFR	65.5 (45.7–82.8)	N/A	

Values expressed as *N* (%) or median (IQR).
eGFR, estimated glomerular filtration rate; mTOR, mammalian target of rapamycin.

Prior to the commencement of the study, no symptomatic SARS-CoV-2 infections were reported by the participants. With regard to absolute immune cell counts at baseline, compared with the dialysis group, the transplant group had significantly higher median absolute $CD8^+$ T-cell counts and lower NK-cell counts pre-Dose 3 ($P < 0.01$) (Supplementary table 1).

Whilst one participant developed antibody-mediated graft rejection in the follow-up period, no participants developed acute transplant rejection within the 6-month period following a vaccine dose or confirmed SARS-CoV-2 infection.

Vaccine schedules

As of March 2021, all transplant recipients and people receiving dialysis in Australia were

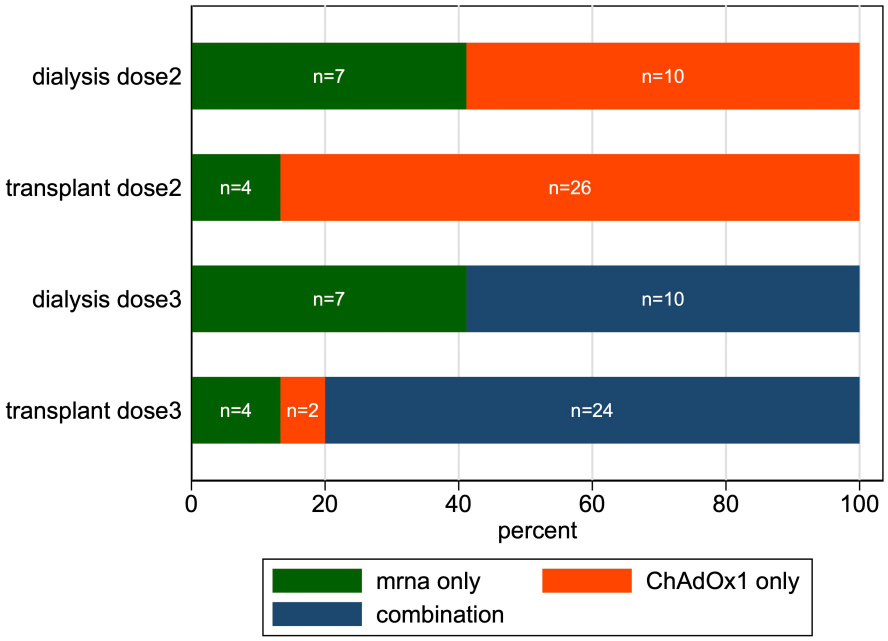

Figure 1. Composition of the two- and three-dose vaccine schedules in the transplant and dialysis groups.

eligible for COVID-19 vaccines. As part of their three-dose primary course, study participants received either homologous mRNA vaccines (two BNT162b2/Pfizer plus a third BNT/162b2/Pfizer or mRNA-1273/Moderna), homologous viral-vector vaccines (three ChAdOx-1) or heterologous vaccines (two viral vector [ChAdOx-1] and one mRNA [BNT/162b2/Pfizer or mRNA-1273/Moderna]) (Figure 1). All doses in our study cohort involved monovalent (ancestral spike protein) vaccines as this predated the availability of bivalent (ancestral and Omicron spike proteins) vaccines.

Most transplant recipients (87%; 26/30) and 59% (10/17) of the dialysis group received ChAdOx1 for their first two doses. Of the 41 participants with post-Dose 3 samples, 21 (78%) participants in the transplant group, and nine (64%) participants in the dialysis group received a regimen of ChAdOx1 and an mRNA (Pfizer or Moderna) vaccine (Figure 1). Two participants in the transplant group received three ChAdOx1 doses, and nine participants (four transplant and five dialysis) had all-mRNA doses. The median time between Dose 2 and sample collection was 32 days (IQR 30–40.5), and the median time between Dose 3 and sample collection was 38 days (IQR 30–54).

Kidney transplant recipients mount lower anti-Spike RBD IgG levels after 2nd and 3rd vaccine doses than people on dialysis

First, we measured the levels of anti-Spike RBD IgG antibodies against the ancestral strain and found that following two vaccine doses, there were fewer responders in the transplant group (56.7%; 17/30) than in the dialysis group (94.1%; 16/17; $P < 0.01$) (Table 2, Figure 2). The median anti-Spike RBD IgG concentrations were significantly lower in the transplant group (1.5 μg mL^{-1}, IQR 0.1–4.2) than in the dialysis group (33.5 μg mL^{-1}, IQR 4.4–125.8; $P < 0.001$).

After three vaccine doses, most of the transplant recipients (85.2%; 23/27) and all dialysis patients achieved a detectable anti-Spike RBD IgG response. The anti-Spike RBD IgG concentrations were significantly higher post-Dose 3 than after Dose 2 in both groups ($P < 0.001$) (Table 2, Figure 2) with a 13-fold increase in the transplant recipients and a threefold increase in the dialysis group.

Higher post-Dose 2 anti-Spike RBD IgG levels strongly positively correlated with higher post-Dose 3 anti-Spike RBD IgG levels in both transplant ($R = 0.78$, $P < 0.001$) and dialysis groups ($R = 0.91$; $P < 0.0001$). Despite this association, the post-Dose 3 median anti-Spike RBD IgG levels

Table 2. Quantification of anti-Spike RBD IgG and neutralising antibodies following Doses 2 and 3

	Transplant			Dialysis		
	Dose 2 (n = 30)	Dose 3 (n = 27)	P-value	Dose 2 (n = 17)	Dose 3 (n = 14)	P-value
Anti-RBD IgG[a]						
Positive, n (%)	17 (56.7)	23 (85.2)	0.009	16 (94.1)	14 (100)	
Median IQR	1.5 (0.1–4.2)	19.9 (0.7–47.8)	< 0.001	33.5 (4.4–125.8)	108.3 (49–207.6)	< 0.001
Ancestral NAb[b]						
Positive, n (%)	8 (27.6)	14 (51.9)	0.66	14 (82.4)	13 (92.9)	0.047
Median IQR	10 (10–23.5)	42.8 (10–154.8)	0.004	80.9 (32.6–277.6)	557 (182.3–2151.5)	< 0.001
Omicron BA.2 NAb						
Positive, n (%)	10 (34.5)	11 (40.7)	0.22	8 (47.1)	11 (78.6)	0.09
Median IQR	10 (10–29.4)	10 (10–75.7)	0.34	10 (10–70.7)	365.6 (103.5–1958.8)	0.001

Statistical analysis: Wilcoxon signed-rank test and chi-squared test.
[a]Anti-spike receptor-binding domain IgG levels. Seropositive cut-off > 0.4 μg mL^{-1}.
[b]Neutralising antibody: Ancestral/Omicron (BA.2) seropositive cut-off, reciprocal dilution IC50 > 20.

were significantly lower in the transplant group (19.9 μg mL^{-1}; IQR 0.7–47.8) than in the dialysis group (108.3 μg mL^{-1}; IQR 49–207.6, $P < 0.001$).

Transplant recipients have poor neutralising antibody responses to ancestral and Omicron BA.2 strains

We determined the titres of NAb against the vaccine-matched ancestral strain and their ability to cross-neutralise the Omicron (BA.2) variant. KTRs achieved a median ancestral NAb titre of 10 (IQR 10–23.5) post-Dose 2, increasing to 42.8 (IQR 10–154.8) post-Dose 3. Comparatively, the dialysis group achieved significantly higher ancestral NAb levels post-Dose 2 (80.9; IQR 32.6–277.6) and post-Dose 3 (557; IQR 182.3–2151.5), $P < 0.01$ (Table 2, Figure 3). Whilst there was a significant increase in NAb levels between Doses 2 and 3 in both groups, fewer transplant recipients achieved detectable ancestral neutralisation levels (51.9%; 14/27) relative to the dialysis group (92.9%; 13/14) after three doses, $P < 0.01$ (Table 2, Figure 3).

Cross-reactive NAb to Omicron (BA.2) variant was observed in 40.7% (11/27) of the transplant group and 78.6% (11/14) of the dialysis group after three doses, $P = 0.02$ (Figure 3). The KTRs median third-dose Omicron NAb level IC50 of 10 (IQR 10–75.7) was below the seropositive cut-off of the assay (IC50: 20). By comparison, the median NAb titre in the dialysis group post-Dose 3 was significantly higher IC50: 365.6 (IQR 103.5–1958.8; $P = 0.002$).

Higher concentrations of post-Dose 3 anti-Spike RBD IgG (ancestral) strongly positively correlated with higher ancestral, and Omicron NAb values in the transplant (ancestral: $R = 0.78$, $P < 0.0001$ and Omicron: $R = 0.72$, $P < 0.0001$) and dialysis (ancestral: $R = 0.78$, $P < 0.001$ and Omicron (BA.2): $R = 0.73$, $P = 0.003$) groups (Supplementary figure 1). Despite a reduction in cross-reactive NAb against Omicron BA.2 in both groups, there was a positive correlation between ancestral NAb and Omicron NAb levels in all participants ($R = 0.9$, $P < 0.0001$). In transplant recipients who mounted an ancestral NAb response (14/27), greater titres of ancestral NAb showed a strong positive correlation with Omicron NAb levels ($R = 0.84$, $P < 0.0001$) (Supplementary figure 2).

Predictors of serological responses to COVID-19 vaccines

Predictors of a positive serological response to a three-dose primary schedule were assessed. ChAdOx1-containing vaccine schedule, higher total cumulative mycophenolate dose (greater than 1 g/day) and lower $CD19^+$ B-cell counts were negative predictors of vaccine responses in KTR (Table 3). When comparing the association between absolute cell counts and responder status, transplant recipients who achieved positive Omicron BA.2 cross-reactive neutralisation levels had significantly higher $CD19^+$ B-cell counts (128 cells μL^{-1}; IQR 120.8–279) than nonresponders (82.8 cells μL^{-1}; IQR 41.6, 126.2; $P = 0.02$) (Supplementary table 2).

Similarly, in the dialysis group, a ChAdOx1-containing vaccine schedule was a predictor of poor serological response. Unlike the transplant group, $CD19^+$ B-cell counts were not predictive of seropositive responses. However, dialysis recipients who had achieved seropositive Omicron NAb levels had significantly lower pre-Dose 3 monocyte

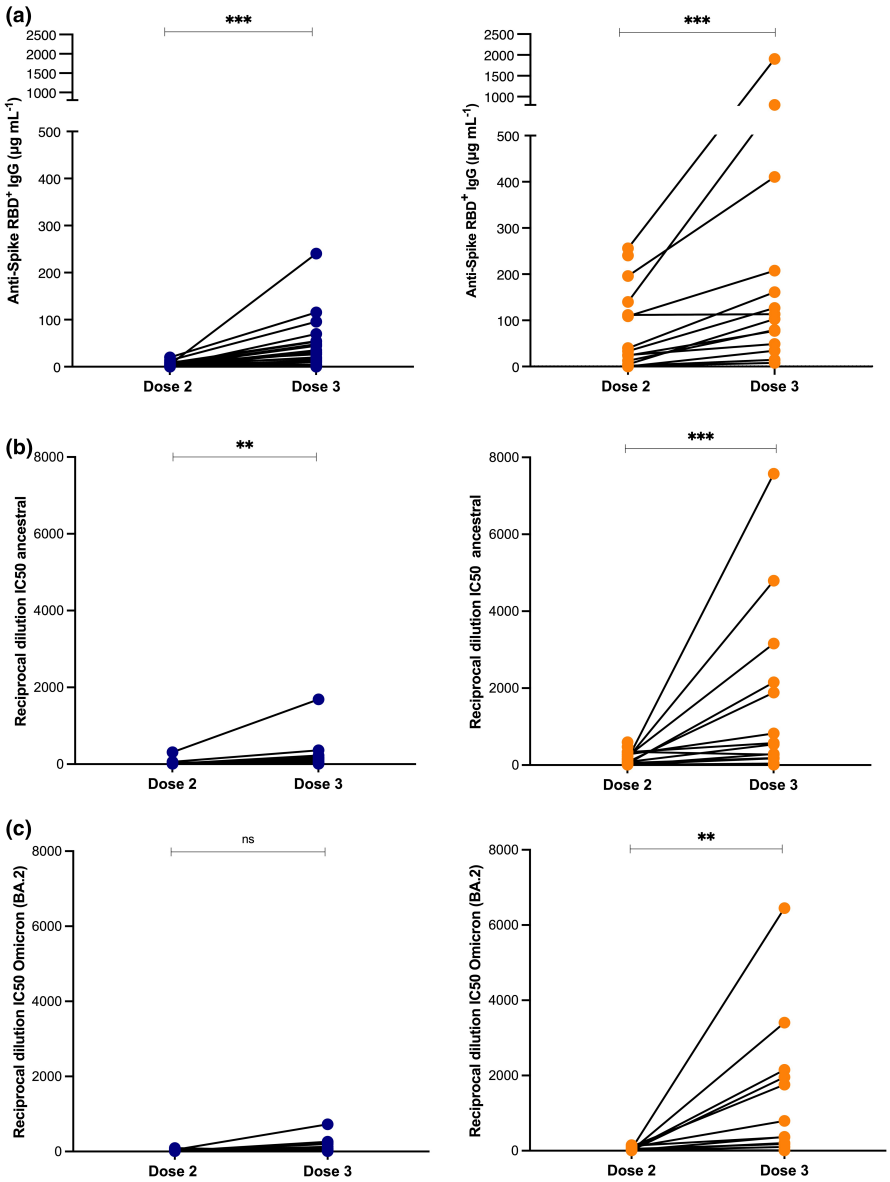

Figure 2. Serological responses to post-Doses 2 and 3, Transplant (left, blue, $n = 27$), Dialysis (right, orange, $n = 14$). **(a)** Anti-Spike RBD IgG (μg mL^{-1}) **(b)** Reciprocal dilution IC50 ancestral NAb, **(c)** Reciprocal dilution IC50 Omicron/BA.2 NAb. Positive cut-off thresholds for Anti-RBD IgG levels and NAb titres are > 0.4 μg mL^{-1} and reciprocal dilution IC50 > 20 respectively. ns = $P \geq 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. Only matched data are shown in these figures, a Dose 3 ancestral and Omicron NAb result from one transplant recipient was not available. Statistical analysis: Wilcoxon signed-rank test.

counts (599.8 cells μL^{-1}; IQR 482.3–670.2) than those who did not (955.7 cells μL^{-1}; IQR 780.2–1396.4; $P = 0.02$) (Supplementary table 3).

There were no other significant differences noted in seroprotection status (anti-Spike RBD IgG and ancestral NAb) and absolute cell counts in this group. Age, gender, KRT vintage and heterologous vaccine schedules were not significantly associated with responder status. Nonresponders had numerically lower median eGFRs than responders, but these were not significant (Table 3).

ChAdOx-1 containing vaccine schedules are associated with poorer serological responses

Given that ChAdOx1 was a predictor of reduced serological responses, we compared the effect of

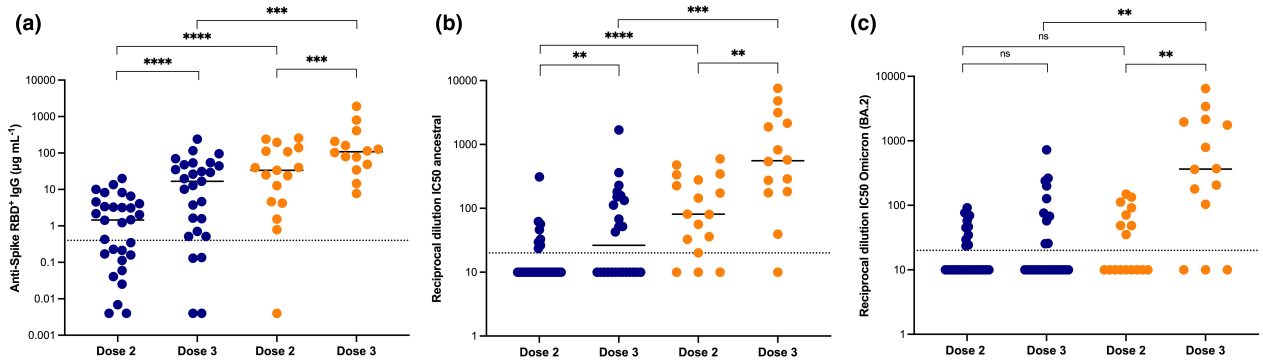

Figure 3. Serological responses post-Doses 2 and 3, Transplant group on the left (blue) and dialysis group on the right (orange). **(a)** Anti-Spike RBD IgG concentrations, **(b)** Reciprocal dilution I50: ancestral Nab, **(c)** Reciprocal dilution IC50: Omicron (BA.2) NAb. Positive cut-off thresholds for Anti-Spike RBD IgG levels and NAb titres are > 0.4 μg mL^{-1} and IC50 > 20, respectively. ns = $P \geq 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$. Statistical analysis: Wilcoxon signed-rank test and Mann–Whitney *U*-test.

vaccine type on seroresponses. To do this, participants were categorised into all-mRNA (homologous) and any-ChADOx-1 groups (homologous and heterologous).

After two doses, there were no significant differences in the anti-Spike RBD IgG, ancestral and Omicron NAb levels between the two vaccine schedule types in the transplant group (Supplementary table 4). Overall, transplant recipients in both vaccine groups mounted poor NAb responses to ancestral and Omicron BA.2 with the median NAb titres below the positive cut-off.

After two doses, the dialysis group who had received homologous ChAdOx1 vaccines generated lower ancestral anti-Spike RBD IgG ($P = 0.001$) and NAb ($P = 0.0001$) responses than those receiving homologous mRNA vaccines (Supplementary table 4). Whilst 71% (5/7) of those who had received all mRNA vaccines, achieved a detectable cross-reactive Omicron NAb response, only 30% (3/10) of dialysis recipients who had received ChAdOx1 vaccines did ($P = 0.09$).

After three doses, the positive anti-Spike RBD IgG response status did not differ significantly between transplant recipients receiving all-mRNA (100%; 4/4) and any ChAdOx1 (83%; 19/23). However, all KTRs receiving mRNA vaccines generated NAbs reactive to both ancestral and Omicron, whereas these were only 43.5% (10/23) and 30.4% (7/23) in the any-ChAdOx1 group, respectively (Supplementary table 4).

Dialysis participants who received three mRNA vaccines had a higher concentration of anti-Spike RBD IgG antibodies than the any-ChAdOx1 group ($P = 0.02$) (Supplementary table 4). All participants in the dialysis group who received a homologous all-mRNA schedule achieved detectable ancestral and Omicron NAb levels. Comparatively, 89% (8/9) and 79% (6/9) in the ChAdOx1 group achieved detectable ancestral and Omicron NAb responses, respectively.

Predicting SARS-CoV-2 breakthrough infection risk according to Dose 3 vaccine response

The relationship between serological vaccine responses and the incidence and severity of SARS-CoV-2 breakthrough infections were assessed in a 12-month follow-up period. Prior to the commencement of the study and during the primary three-dose vaccination schedule period, no symptomatic COVID-19 infections were reported by the participants. All reported COVID-19 infections occurred in the 12-month study follow-up period after the participants' third vaccine dose and corresponding study sample collection. Fourteen participants (47%) in the transplant group and five (29%) in the dialysis group experienced a breakthrough infection following vaccine Dose 3 (Table 4). The dialysis group had no episodes of hospitalisation or death whilst there were four hospitalisations (13.3%) and one death (3.3%) in the transplant group. Within the dialysis group, two of the five infections occurred after receiving a kidney transplant during the follow-up period.

The median Dose 3 anti-Spike RBD IgG concentrations and NAb titres were lower in those who had developed breakthrough infections than those who had not; however, the differences were

Table 3. Predictors of positive serological responses in transplant recipients

	Responder	Nonresponder	*P*-value
Anti-RBD IgG	*n* = 23	*n* = 4	
Age (years)	60 (56.7–63.6)	64.7 (54.7–66.7)	0.39
Female (%)	5 (21.7%)	2 (50%)	0.23
eGFR[a] mL/min/1.73 m^2	67.4 (53.1–82.8)	52.7 (39.1–79.2)	0.47
KRT[b] years	5.0 (3.1–9.8)	5.6 (0.9–11.7)	0.64
MMF[c] > 1 g per day	11 (47.8%)	4 (100%)	0.047
Any-ChAdOx1	19 (82.6%)	4 (100%)	0.37
Mixed schedule	17 (73.9%)	4 (100%)	0.25
B-cell count[d]	122 (86.1–180.9)	43.5 (40.9–181.8)	0.35
Ancestral NAb (> 20)	*n* = 14	*n* = 13	
Age (years)	62.1 (58.5–64)	57.9 (52.5–66.5)	0.46
Female (%)	2 (14.3)	5 (38.5)	0.15
eGFR mL/min/1.73 m^2	67.6 (53.1–83.1)	59.6 (41.3–84.1)	0.46
KRT years	8 (3.2–11)	3.6 (1.8–7.6)	0.14
MMF > 1 g per day	8 (57.1%)	7 (53.9)	0.86
Any-ChAdOx1	10 (71.4%)	13 (100%)	0.04
Mixed schedule	10 (71.4%)	11 (84.6%)	0.41
B-cell count	127.2 (97.2–256.2)	112.8 (43.5–129.8)	0.08
Omicron NAb (> 20)	*n* = 11	*n* = 16	
Age (years)	60.1 (57.6–65.2)	60.5 (54.1–65.4)	0.75
Female (%)	1 (9%)	6 (37.5%)	0.10
eGFR mL/min/1.73 m^2	67.9 (45.4–80.3)	60.7 (47.6–84.8)	0.72
KRT years	7.9 (3.3–9.9)	4.3 (1.6–9.6)	0.34
MMF > 1 g per day	7 (63.6%)	8 (50%)	0.48
Any-ChAdOx1	7 (63.6%)	16 (100%)	0.01
Mixed schedule	7 (63.6%)	14 (87.5%)	0.14
B-cell count	128 (120.9–279)	82.8 (41.6–126.2)	0.02

[a]eGFR—Estimated glomerular filtration rate (mL/min/1.73 m^2).
[b]KRT—Kidney replacement therapy (total transplant time, total dialysis time).
[c]MMF—Mycophenolate.
[d]$CD19^+$ B-Lymphocyte count (cells μL^{-1}).

Table 4. Summary of SARS-CoV-2 breakthrough infections and COVID-19 outcomes

	Transplant *n* = 30	Dialysis *n* = 17
Total infections	14 (47%)	5 (29%)
Number vaccines before infection		
3	3	3
4	8	2
5	3	–
Hospitalisation	4 (13.3%)	0
Hospital LOS (days)[1]	3.25 ± 1.31	0
Death	1 (3.3%)	0
Re-infection	1 (3.3%)	0

Values expressed as *N* (%) or mean and std dev. Two dialysis participants had confirmed infections after they had received a kidney transplant during the study follow up period.
LOS, Length of stay.

not statistically significant (Supplementary table 5). Given the low number of infections in the dialysis group, they were not analysed separately.

When comparing the change in antibody responses between Doses 2 and 3, those who had developed breakthrough infections had a significantly lower change in the anti-Spike RBD IgG concentrations (4.45 $\mu g\ mL^{-1}$; IQR 0.5–41.5 compared to 41.2 $\mu g\ mL^{-1}$; IQR 11.1–87.8; $P = 0.04$) and ancestral NAb titres (change in IC50: 2.5; IQR −5.7 to 136.7 compared to 133.5; IQR 14–524.1; $P = 0.050$) than those who had not. Whilst there was a lower median change in Omicron NAb titres in the breakthrough infection group than those without infection (change in IC50: 0; IQR −17.5 to 175.3 compared to change in IC50: 49.5; IQR 0–327.7; $P = 0.23$), the difference was not statistically significant.

Six (32%) participants with breakthrough infection had less than 1 $\mu g\ mL^{-1}$ change in anti-Spike RBD IgG, including two participants (11%) who had a reduction in their anti-Spike RBD IgG values post-Dose 3 compared to Dose 2. Eight

participants (42%) with breakthrough infection had either no change or a decrease in ancestral NAb titres between time points, and nine participants (47%) had no change or a decrease in Omicron NAb titres between time points. By comparison, of those without breakthrough infection, only 7% (2/28) had minimal change in the anti-Spike RBD IgG concentration, and 18% had minimal change or a decrease in the ancestral NAb titre between doses.

We assessed the relationship between absolute cell counts and the risk of breakthrough infection. In the dialysis group, absolute cell counts post-Dose 2 did not predict breakthrough infections; however, transplant recipients who contracted SARS-CoV-2 had significantly higher $CD8^+$ T-cell counts pre-Dose 3 (747.58 cells μL^{-1}; IQR 613.4–1395.4 compared to 551 cells μL^{-1}; IQR 253–788.5; $P = 0.03$).

DISCUSSION

Our study highlights the continued risk posed by SARS-CoV-2 infection in transplant recipients despite a three-dose primary vaccine schedule, emphasising the need for ongoing vigilance in this susceptible group. KTRs mounted significantly weaker antibody responses than their dialysis counterparts, requiring one more vaccine to achieve a similar serological response.

Our cohorts received the original monovalent vaccine, which only contained the ancestral spike protein.[26] The Omicron variant has been identified as the most divergent variant with over 50 identified mutations, and the majority affecting the spike protein.[27] The majority of the KTRs generated detectable ancestral anti-Spike RBD IgG; however, in most participants, this did not translate to the production of functional NAb that would confer protection, nor cross-neutralisation against the Omicron variant. The measurement of IgG antibodies alone may not accurately depict the level of protection against mild or severe COVID-19 disease. Other immunoglobulin isotypes, such as mucosal anti-Spike IgA and neutralising IgA antibodies have been described as playing a key role in protection against respiratory viruses, including SARS-CoV-2.[28,29] Additionally, their levels are noted to be boosted by the COVID-19 vaccine.[28,29] The neutralisation assay used in our study captures all NAb irrespective of isotype.

The higher likelihood of seroconversion in people receiving dialysis highlights the importance of ensuring that all dialysis recipients who are on the transplant wait list are adequately vaccinated against COVID-19 before transplantation thus optimising protection against mild and severe disease. This is especially important given the high burden of immunosuppression in the acute post-transplant period, limiting effective vaccine responses, and significantly increasing the risk of poor COVID-19 outcomes.[30]

Several studies also show comparable immune responses between people on dialysis and individuals without kidney disease; however, the durability of response and SARS-CoV-2 infection outcomes remain poor in dialysis recipients.[7,31] Thus, despite these promising results, dialysis recipients may still have poorer clinical outcomes compared to those without CKD.

In our study, we have demonstrated that even low cumulative doses of MMF (> 1 g) can negatively impact serological responses. The use of MMF, particularly at higher cumulative doses (> 1.5 g), has been described to be associated with diminished postvaccine antibody responses following COVID-19 and other vaccines.[32–34] Dose reduction and/or withholding of MMF is a common part of the treatment strategy with SARS-CoV-2 infections in SOT recipients.[35–37] Further research may shed light on the utility of temporarily withholding or significantly reducing the cumulative MMF dose in the perivaccination period to optimise seroconversion rates in KTRs.[33,38] However, optimising seroconversion needs to be weighed against the risk of graft rejection.

Vaccine and vaccine schedule types (homologous or heterologous) have been shown to impact vaccine-induced immunogenicity. Many COVID-19 vaccine immunogenicity studies largely describe responses with mRNA vaccines or other viral vector vaccines (Jannsen/Johnson & Johnson), our study focusses on ChAdOx1 vaccines, which was the predominant vaccine delivered in the early phase of the vaccine programme in Australia.[39,40] Our findings support current local and international Nephrology guidelines favoring mRNA vaccines. Current evidence suggests enhanced immunogenicity with heterologous vaccination schedules.[24,25,33] Whilst homologous ChAdOx1 containing vaccine schedules have consistently been shown to illicit weaker serological immune responses than a homologous or heterologous mRNA vaccine schedule.[24,25,41] This was replicated in our study as the homologous mRNA vaccine schedule was found to be superior to a ChAdOx1 containing schedule in both groups, particularly in achieving a cross-reactive Omicron

NAb response. Whilst the dialysis cohort achieved favorable results compared to KTRs, those who had received a ChAdOx1 containing vaccine schedule had significantly impaired Omicron neutralisation. This is of particular significance given the rapid evolution of viral variants. The results also have implications for vaccine selection for future pandemics.[24,25,39]

Higher $CD19^{+}$ B-cell counts and lower monocytes counts were associated with achieving seropositive responses in our transplant and dialysis groups, respectively. A higher total B-cell count may suggest a larger reservoir of cells with the capacity to recognise the virus and mounting an antibody response. This, however, requires further investigation. In our dialysis cohort, the association observed between increased absolute monocyte counts and reduced NAb could be because of the state of chronic inflammation experienced by people receiving dialysis, which in turn can impact their immune profile.[42] Counter-regulatory immune mechanisms play a part in augmenting the vaccine-induced immune responses.[43] Our findings align with that of Valentini *et al*. who reported higher inflammatory monocyte levels in people receiving dialysis who had blunted serological responses to COVID-19 vaccines.[44]

Additional predictors of serological responses including older age, transplant/dialysis duration and poorer renal function (low eGFR) were not found to be significant predictors in our study cohort.[7,20,25,41,45] In our study, nonresponders had lower median eGFR values; however, this did not reach statistical significance, low participant numbers, particularly those with more significant renal impairment, may have precluded findings any significant differences.

The impaired serological immune responses in our transplant cohort, particularly cross-reactive NAb responses against the Omicron BA.2 VOC, emphasised the long-term risk of severe COVID-19 disease from breakthrough infections. Additionally, the risk was likely underestimated as two of the participants who had contracted SARS-CoV-2 infection in the dialysis group, did so after receiving a transplant in the follow-up period. Interestingly, the absolute serological response postvaccine did not predict breakthrough infection and disease severity; however, change in antibodies between doses did. This parameter could help identify individuals who are poorly protected against infection and at risk of severe disease and death. Unexpectedly, poorer Omicron NAb response did not correlate with a greater risk of breakthrough infections. However, as most of the transplant cohort were nonresponders, the numbers may have been too small to determine a significant impact of Omicron NAb seroresponses on breakthrough infection outcomes.

Our study echoes findings from the literature supporting the safety of vaccination, with no increased risk of transplant rejection with guideline-recommended vaccination, including the COVID-19 vaccine.[46–48] We previously reported the barriers and enablers to the COVID-19 vaccine uptake in KTRs.[49] Concerns with regard to vaccine safety, particularly the risk of transplant rejection, was identified as a major barrier to the COVID-19 vaccine uptake in KTRs.[49] Several case reports have described episodes of acute allograft rejection following COVID-19 vaccination and infection.[47,50–52] The risk–benefit ratio favors vaccination, given the clear risk of severe SARS-CoV-2 infection and death in KTRs.[1,2]

There are some limitations to our study. These include relatively small patient numbers with some participants lost to follow-up after the third vaccine dose. Small numbers may have resulted in Type II errors in finding explanatory factors or differences between groups. Participant recruitment was hindered by the COVID-19 lockdown and strict travel restrictions limiting attendance to Monash Health for sample collection. Participants already attending Monash Health for treatment and care were able to participate in the study. During the study, there were several vaccine-related policy changes owing to rising SARS-CoV-2 infection numbers that led to some heterogeneity in the interval between vaccine doses. These differences may have impacted the antibody responses. However, it should be noted that the median time to sample collection postvaccination was not statistically significantly different between the groups.

The small number of transplant recipients with low eGFR made it difficult to fully examine the impact of impaired renal function on vaccine antibody responses. Total immunoglobulin levels and subtypes (IgG) were not measured in our study participants. Whilst IgG levels could identify participants with a humoral deficiency (primary or secondary) who are at risk of mounting poor serological responses, neutralising antibody levels have been shown to be a more specific and reliable correlate of immune protection against SARS-CoV-2 infection.[53,54]

In the follow-up period, most participants have had additional booster doses (up to five vaccines in total), which may have affected infection

outcomes. However, it is important to note that despite having poorer COVID-19 outcomes as compared to their dialysis counterparts, a greater proportion of transplant recipients had either a fourth or fifth COVID-19 booster vaccine prior to a confirmed SARS-CoV2 infection. No one in the dialysis group had a fifth booster dose before a confirmed breakthrough infection. Asymptomatic SARS-CoV-2 infections may have been missed in the transplant cohort as the testing was usually prompted by clinical symptoms or contact with SARS-CoV-2-confirmed cases.

Recent studies have described antibody responses to fourth booster dose in people with CKD.[55,56] Understanding the serological and cellular responses in KTRs, dialysis and CKD population beyond the initial primary vaccine schedule (e.g. Doses 4 or more) is essential to inform schedule recommendations and clinical care. As part of a larger multicentre study assessing COVID-19 vaccine responses in different vulnerable and immunocompromised cohorts (HIV, inflammatory bowel disease, lung transplant and others), we will be assessing immune responses to regular booster doses and more recently circulating variants (e.g. XBB1) in people with CKD stages 4/5, end-stage renal failure requiring dialysis and KTRs.

METHODS

Participant recruitment

This study was a prospective, single-centre, observational pilot study assessing serological vaccine responses to a three-dose primary vaccination schedule in dialysis and KTRs. Adults (18–70 years) receiving haemodialysis or with a kidney-only or combined kidney and pancreas transplant were eligible. The study period was between 21 July 2021 and 25 August 2022. Participants were recruited from Monash Health, a 1500-bed tertiary hospital caring for approximately 700 dialysis and 1100 KTRs. Exclusion factors were as follows: severe vaccine allergies or known contraindications to vaccination; transplant duration < 6 months or > 20 years; ABO incompatible transplantation; immunosuppression changes or episodes of rejection or serious infection in the preceding 3 months; or receiving a maintenance mycophenolate dose > 1.5 g/day. All participants provided written informed consent. This study was conducted according to the Declaration of Helsinki and approved by the Monash Health Human Research Ethics Committee (HREC/74604/MonH-2021-264 994). All participants were followed for 1 year from study completion to identify breakthrough SARS-CoV-2 infections and transplant rejection. The study and follow-up periods included several Omicron waves in Australia (subvariants BA.1/BA.2/BA.3/BA.4/BA.5), which occurred between December 2021 and September 2023.[57]

Sample collection and processing

Blood samples were collected 3–5 weeks after receiving the second and third COVID-19 vaccine doses. The absolute counts of $CD4^+$ and $CD8^+$ T cells, B cells, NK cells, monocytes and granulocytes in whole blood were quantified using BD TruCount™ tubes (Becton, Dickinson and Company BD Biosciences, San Jose, California, USA).[58–60] Plasma was collected and live peripheral blood mononuclear cells were isolated via standard Ficoll–Paque (Cytvia, Marlborough, Massachusetts, USA) gradient centrifugation and cryogenically stored. Plasma was used for the evaluation of antibody responses to SARS-CoV-2 infection and vaccination.

Measurement of SARS-CoV-2 anti-Spike receptor-binding domain IgG

The quantification of anti-Spike RBD IgG antibodies in plasma was measured by ELISA as previously described.[58–60] The limit of detection was 0.1 μg, and a positive response was defined to be > 0.4 μg mL^{-1}.

Measurement of SARS-CoV-2 neutralising antibodies

The measurement of NAb was performed using SARS-CoV-2 retroviral pseudotyped particles as previously described.[58–60] Neutralising antibody activity against the original ancestral and Omicron (BA.2) strains was assessed. The assay included monoclonal NAb with known IC50 against VOCs. Neutralising antibody titres are expressed as the reciprocal dilution of plasma required to inhibit virus entry by 50%. Neutralising antibody titres ≥ 20 were considered positive.

Statistical analysis

Continuous variables were expressed as median and interquartile range or mean and standard deviation as appropriate. Categorical variables were expressed as number (*n*) and proportion (%). Differences in means were assessed using the Student's *t*-test, differences in medians by the Mann–Whitney *U*-test, Wilcoxon signed-rank test and Kruskal–Wallis test and differences in proportions by the chi-squared test or two-tailed Fisher's exact test. Correlation between continuous variables was assessed using the Spearman's correlation coefficient. Paired data were analysed using Wilcoxon signed-rank test. All analyses were conducted using STATA version 17.0 (College Station, TX, USA) and GraphPad Prism 9. Power calculations were not performed for this pilot study. In all analyses, *P*-values < 0.05 were considered to be significant.

Primary outcomes

The primary outcome measures were antibody responses as characterised by anti-Spike RBD IgG levels and reciprocal neutralising antibody titres to ancestral and Omicron (BA.2) strains and subsequent clinical SARS-CoV-2 infections. Participants were categorised into 'responder' and

'nonresponder' groups according to whether they had achieved the target threshold for positive anti-Spike RBD IgG levels ($> 0.4\ \mu g\ mL^{-1}$) or NAb titres (reciprocal dilution IC50 > 20). SARS-CoV-2 infections were defined by a positive diagnostic test (polymerase chain reaction [PCR] and/or rapid antigen test [RAT]) with or without associated clinical symptoms. SARS-CoV-2 infection testing was performed in those with clinical symptoms, and/or those who had contact with confirmed SARS-CoV-2 cases. Additionally, the dialysis group had asymptomatic screening (RAT/PCR) during their dialysis sessions, as part of routine infection prevention procedures.

Secondary outcomes

Secondary outcomes were antibody responses according to vaccine type (ChAdOx1-containing or all-mRNA vaccine schedule) and predictors of poor responses (estimated glomerular filtration rate [eGFR], age, gender, kidney replacement therapy [KRT] vintage, ChAdOx1-containing vaccine schedule, mycophenolate cumulative dose, and heterologous or homologous vaccination schedules).

Conclusion

Serological responses to COVID-19 vaccines in KTRs lag behind their dialysis counterparts. Higher cumulative mycophenolate dose, ChAdOx1-containing vaccine schedule, lower $CD19^{+}$ count and higher monocyte count were associated with poorer antibody responses. KTRs remained at high risk of breakthrough infection after their primary vaccination schedule, underlining their need for booster doses, strict infection prevention measures and close surveillance. Vaccine responses, particularly the change between doses could assist with optimising care including timing and number of booster doses, monitoring, prophylaxis and therapeutic options for breakthrough infections.

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AUTHOR CONTRIBUTIONS

Dhakshayini Tharmaraj: Conceptualization; data curation; formal analysis; investigation; project administration; visualization; writing – original draft; writing – review and editing. **Irene Boo:** Investigation; methodology. **Jessie O'Hara:** Investigation; methodology. **Shir Sun:** Investigation; methodology. **Kevan R Polkinghorne:** Supervision; writing – review and editing. **Claire Dendle:** Supervision; writing – review and editing. **Stephen J Turner:** Resources; supervision. **Menno C van Zelm:** Funding acquisition; resources; supervision; writing – review and editing. **Heidi E Drummer:** Funding acquisition; resources; supervision; writing – review and editing. **Gabriela Khoury:** Conceptualization; funding acquisition; investigation; methodology; supervision; writing – original draft; writing – review and editing. **William R Mulley:** Conceptualization; formal analysis; funding acquisition; resources; supervision; writing – original draft; writing – review and editing.

CONFLICT OF INTEREST

MCvZ is an inventor on a patent related to this work. The other authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.