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BRIEF COMMUNICATION

Heterologous Ad.26.COV2.S versus homologous BNT162b2/mRNA-1273 as a third dose in solid organ transplant recipients seronegative after two-dose mRNA vaccination

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Abstract

Heterologous vaccination ("mixing platforms") for the third (D3) dose of SARS-CoV-2 vaccine is a potential strategy to improve antibody responses in solid organ transplant recipients (SOTRs), but data are mixed regarding potential differential immunogenicity. We assessed for differences in immunogenicity and tolerability of homologous (BNT162b2 or mRNA-1273; D3-mRNA) versus heterologous (Ad.26.COV2.S; D3-JJ) D3 among 377 SARS-CoV-2-infection naïve SOTRs who remained seronegative after two mRNA vaccines. We measured anti-spike titers and used weighted Poisson regression to evaluate seroconversion and development of high-titers, comparing D3-JJ to D3-mRNA, at 1-, 3-, and 6 month post-D3. 1-month post-D3, seroconversion (63% vs. 52%, $p = .3$) and development of high-titers (29% vs. 25%, $p = .7$) were comparable between D3-JJ and D3-mRNA recipients. 3 month post-D3, D3-JJ recipients were 1.4-fold more likely to seroconvert (80% vs. 57%, weighted incidence-rate-ratio: wIRR = $_{1.10}1.40_{1.77}$, $p = .006$) but not more likely to develop high-titers (27% vs. 22%,

Abbreviations: D2, dose 2; D3, dose 3; EIA, enzyme immunoassay; MMF, mycophenolate; mRNA, messenger RNA; RBD, receptor binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOTRs, solid organ transplant recipients; wIRR, weighted incidence-rate-ratio.

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wIRR = $_{0.44}0.92_{1.93}$, $p = .8$). 6 month post-D3, D3-JJ recipients were 1.41-fold more likely to seroconvert (88% vs. 59%, wIRR = $_{1.04}$ $1.41_{1.93}$, $p = .029$) and 2.63-fold more likely to develop high-titers (59% vs. 21%, wIRR = $_{1.38}2.63_{5.00}$, $p = .003$). There was no differential signal in alloimmune events or reactogenicity between platforms. SOTRs without antibody response after two mRNA vaccines may derive benefit from heterologous Ad.26.COV2.S D3.

KEYWORDS
antibodies, heterologous, SARS-CoV-2, transplant, vaccine

1 | INTRODUCTION

SARS-CoV-2 infection causes substantial morbidity and mortality in solid organ transplant recipients (SOTRs).[1-4] Vaccination holds promise to reduce COVID-19 severity in SOTRs, but a significant subset does not develop antibody response after two- and three-dose mRNA vaccine series,[5-8] which likely contributes to higher rates of COVID-19 breakthrough after vaccination.[4] Heterologous vaccination ("mixing platforms") is one potential mode to augment aspects of immune sero-response,[9-12] but data are limited in SOTRs.[13-15] In one randomized trial of kidney transplant recipients who remained seronegative after two mRNA vaccine doses, seroconversion rates 1 month after receiving Ad.26.COV2.S as a third dose (D3) was no different than after receiving a homologous mRNA vaccine.[16] However, studies in the general population indicate that SARS-CoV-2 binding antibody and neutralization might demonstrate a delayed increase after Ad.26.COV2.S.[17-19] It is therefore possible that a difference in vaccine immunogenicity could emerge beyond the early timepoint of 1-month after receipt of an Ad.26.COV2.S when compared with an additional mRNA vaccine as D3 in vulnerable SOTRs.

The primary goal of this study was to compare the antibody kinetics after D3 with Ad.26.COV2.S (D3-JJ) versus an mRNA vaccine (D3-mRNA) up to 6 month post-D3 in a large real-world cohort of SOTR who remained seronegative after receiving two mRNA SARS-CoV-2 vaccines. Vaccine reactogenicity, alloimmune complications, and incidence of breakthrough infections were also assessed between D3-JJ and D3-mRNA recipients.

2 | METHODS

2.1 | Study population

Adult (age ≥ 18 years) SOTRs across the US were recruited for our national observational study as previously described.[6,7] 377 SOTRs remained seronegative on an anti-spike assay at least 1 month after two homologous mRNA vaccines (BNT162b2 or mRNA-1273), and they subsequently reported receiving a third dose of BNT162b2 or mRNA-1273 (D3-mRNA) or Ad.26.COV2.S (D3-JJ) between March 30, 2021–January 13, 2022. Participants taking belatacept were excluded from this cohort due to established poor global vaccine sero-responses ($n = 39$),[20] as were those reporting SARS-CoV-2 infection prior to D3 or with unknown date of infection ($n = 85$), and those who reported receiving monoclonal antibodies prior to D3 ($n = 6$). This study was approved by the Johns Hopkins University Institutional Review Board (IRB00248540) and participants provided electronic informed consent.

2.2 | Measurement of post-vaccination immunogenicity

Anti-spike titers were measured pre-D3 and 1-month (14–45 days, $n = 304$ measurements), 3-month (60–120 days, $n = 272$ measurements), 6-month (135–210 days, $n = 93$ measurements) post-D3 using one of two clinical assays: the Roche Elecsys® anti-SARS-CoV-2 S enzyme immunoassay (EIA), testing for total antibody to the SARS-CoV-2 S-receptor binding domain protein (anti-RBD, range < 0.8, 2500 U/ml, seropositive: ≥0.8 U/ml), or the EUROIMMUN EIA, testing for S1 domain of the SARS-CoV-2 spike protein (anti-S1, range 0.1, >8.94 arbitrary units [AU], seropositive: ≥1.1 AU). The anti-S1 assay was used for a minority of recipient samples in both vaccine groups at each timepoint: pre-D3 (43% D3-JJ vs. 42% of D3-mRNA samples), 1-month post-D3 (37% vs. 34%), 3 month post-D3 (33% vs 35%), and 6 month post-D3 (29% vs 24%), with the remainder tested by anti-RBD. Both assays have demonstrated good correlation with surrogate and live virus neutralization in SOTRs,[21-23] including anti-S1 ≥ 4 AU and anti-RBD ≥ 250 U/ml each corresponding to a threshold of neutralization of ancestral SARS-CoV-2 variants (defined hereafter as "high-titer") (Figure S1). Antibody measurements were excluded after a participant reported any additional vaccine doses ($n = 149$), monoclonal antibodies ($n = 103$), or developed incident COVID-19 ($n = 40$), as identified through scheduled serial cohort survey (see Section 2.6).

2.3 | Comparing post-vaccination antibody kinetics between heterologous and homologous vaccine platforms

Poisson regression with robust standard error was used to evaluate seropositivity (anti-RBD ≥ 0.8 U/ml or anti-S1 ≥ 1.1 AU) or

development of high-titers (anti-RBD ≥ 250 U/ml or anti-S1 ≥ 4 AU), comparing D3-JJ recipients to D3-mRNA recipients at 1-, 3-, and 6 month post-D3, after weighting for age (doubly-robust) and organ received (kidney vs. no-kidney). Separate weights were computed for each time point. We assessed the standardized differences of the weighted populations at 1, 3, and 6 months to confirm that the weighted populations were comparable in terms of age and organ received at each time point.

2.4 | Sensitivity analysis

We repeated analyses stratified by assay type for each time point post hoc as sensitivity analysis to assess whether inferences differed. Similar to the primary analysis, Poisson regression with robust standard error was used to evaluate both seropositivity and development of high-titers, comparing D3-JJ recipients to D3-mRNA recipients at 1, 3, and 6 month post-D3 using either anti-RBD or anti-S1 assays. As in the main analysis, we weighted for age and organ type (kidney vs. no-kidney), except for 3 month post-D3 (only weighted for age) and 6 month post-D3 (unweighted) among participants tested with anti-S1 due to sample size constraints.

2.5 | Subgroup analysis among D3-mRNA recipients

Among the D3-mRNA recipients, a subgroup analysis compared the post-D3 seropositivity and development of high-titers between recipients of three consecutive BNT162b2 vaccines to recipients of three consecutive mRNA-1273 vaccines using Fisher's exact test.

2.6 | Vaccine safety and adverse reactions during observation

Serial follow up surveys were used to ascertain serious adverse events after vaccination (collected at 1-week post-D3), including alloimmune complications such as rejection, as well as incident myocarditis, anaphylactoid reactions, or thrombotic events including vaccine-induced thrombotic thrombocytopenia (VITT). Incident COVID-19 diagnoses or reception of monoclonal antibodies were also ascertained by scheduled follow-up survey, including two additional surveys during the omicron wave (January 2022).

2.7 | Statistical analysis

Differences in population characteristics and local or systemic post-vaccination adverse reactions between D3-JJ and D3-mRNA were compared using Wilcoxon rank-sum test for continuous variables, and Fisher's exact test for binary or categorical variables. Confidence intervals were presented as per the method of Louis and Zeger.[24] All analyses were performed using Stata/MP 17.1 (College Station, TX). Results were reported with two-sided $p < .05$ as level of significance.

3 | RESULTS

3.1 | Study population

Among 377 SOTRs, the 40 D3-JJ recipients and 337 D3-mRNA recipients were similar in terms of sex (48% female vs 59% female, $p = .18$), years since transplant (median [IQR] 6 [3, 12] years vs 5 [2, 9] years, $p = 22$), and mycophenolate (MMF) usage (88% vs 85%, $p = .8$), but D3-JJ recipients were slightly older (median [IQR] 67 [55–71] vs. 62 [49–68] years, $p = .058$) and more likely to have received a kidney transplant (83% vs. 61%, $p = .009$); these factors were therefore weighted as described above (Table 1). Median (IQR) time from the second dose to the third dose was 90 (65–108) days for the D3-JJ recipients, and 168 (143–188) days for D3-mRNA recipients ($p < .001$). Median (IQR) time from the second dose to measurement of pre-D3 antibody was 72 (32–94) for D3-JJ recipients, and 99 (85–166) for D3-mRNA recipients ($p < .001$).

3.2 | Post-vaccination kinetics comparing heterologous and homologous vaccine platforms

At 1-month post-D3, 63% (22/35) of D3-JJ recipients and 52% (141/269) of D3-mRNA recipients became seropositive ($p = .28$, Table 2); this difference did not reach statistical significance in weighted analysis (weighted incidence-rate-ratio [wIRR] = $_{0.98}1.29_{1.69}$, $p = .064$, Table 3). High-titer response at 1-month post-D3 occurred in 29% (10/35) of D3-JJ recipients and 25% (66/269) of D3-mRNA recipients ($p = .7$); this difference did not reach statistical significance in the weighted analysis (wIRR = $_{0.91}1.57_{2.70}$, $p = .10$) (Tables 2 and 3).

At 3 months post-D3, 80% (24/30) of D3-JJ recipients and 57% (139/242) of D3-mRNA recipients were seropositive ($p = .018$, Table 2); D3-JJ recipients were 1.4-fold more likely to be seropositive (wIRR = $_{1.10}1.40_{1.77}$, $p = .006$, Table 3). High-titer response at 3 month post-D3 occurred in 27% (8/30) of D3-JJ recipients and 22% (53/242) of D3-mRNA recipients ($p = .64$); this difference did not reach statistical significance (wIRR = $_{0.44}0.92_{1.93}$, $p = .8$) (Tables 2 and 3).

At 6 month post-D3, 88% (15/17) of D3-JJ recipients and 59% (45/76) of D3-mRNA recipients were seropositive ($p = .026$, Table 2); D3-JJ recipients were 1.41-fold more likely to be seropositive (wIRR = $_{1.04}1.41_{1.93}$, $p = .029$, Table 3). High-titer response at 6 months post-D3 occurred in 59% (10/17) of D3-JJ recipients and 21% (16/76) of D3-mRNA recipients ($p = .005$); D3-JJ recipients were 2.63-fold more likely to develop high-titers at 6 months as compared to D3-mRNA recipients (wIRR = $_{1.38}2.63_{5.00}$, $p = .003$) (Tables 2 and 3).

TABLE 1 Population characteristics

	D3-mRNA ($n = 337$)	D3-JJ ($n = 40$)	p
Age, median years (IQR)	62 (49, 68)	67 (55, 71)	0.058
Female (n, %)	197 (58.8%)	19 (47.5%)	0.18
Non-White race (n, %)[a]	36 (10.7%)	0 (0%)	0.022
Hispanic (n, %)[a]	12 (3.6%)	3 (7.5%)	0.21
Years since transplant at first dose, median (IQR)	4.6 (1.8, 9.0)	5.6 (2.5, 11.6)	0.22
Steroid use (n, %)	223 (66.2%)	32 (80.0%)	0.11
Tacrolimus (n, %)	297 (88.1%)	34 (85.0%)	0.61
MMF use (n, %)	285 (84.6%)	35 (87.5%)	0.82
mTOR inhibitors (n, %)	37 (11.0%)	4 (10.0%)	>0.99
Triple immunosuppression[b] (n, %)	175 (51.9%)	24 (60.0%)	0.40
Organ transplanted (n, %)			
Kidney	187 (55.5%)	30 (75.0%)	0.033
Liver	38 (11.3%)	0 (0%)	
Pancreas	2 (0.6%)	0 (0%)	
Lung	51 (15.1%)	2 (5.0%)	
Heart	37 (11.0%)	4 (10.0%)	
Multi-organ	22 (6.5%)	4 (10.0%)	
Any kidney transplant (n, %)	207 (61.4%)	33 (82.5%)	0.009
Initial vaccines received (n, %)			0.12
Two-dose BNT162b2	220 (65.3%)	21 (52.5%)	
Two-dose mRNA–1273	117 (34.7%)	19 (47.5%)	
D2 to pre-D3 titer, median days (IQR)	99 (85, 166)	72 (32, 94)	<0.001
D2 to D3, median days (IQR)	168 (143, 188)	90 (65, 108)	<0.001
Pre-D3 titer to D3, median days (IQR)	40 (6, 86)	13 (1, 30)	<0.001
D3 to 1-month titer, median days (IQR)	29 (21, 33) ($n = 269$)	30 (22, 32) ($n = 35$)	0.95
D3 to 3-month titer, median days (IQR)	92 (90, 96) ($n = 242$)	92 (90, 96) ($n = 30$)	0.92
D3 to 6-month titer, median days (IQR)	182 (161, 184) ($n = 76$)	178 (165, 183) ($n = 17$)	0.44
Rejection in 6-month pre-D3 (n, %)	5 (1.5%)	0 (0%)	>0.99
Rejection after D3 (n, %)	1 (0.3%)	0 (0%)	>0.99

Abbreviations: D2, second mRNA vaccine; D3, third vaccine; MMF, mycophenolic acid or mycophenolate mofetil.

[a]One participant did not respond to race, and three participants did not respond to ethnicity.

[b]Triple immunosuppressants include: steroids, calcineurin-inhibitors, anti-metabolites.

3.3 | Sensitivity analysis

Using only samples tested on the anti-RBD assay, D3-JJ recipients were more likely than D3-mRNA recipients to be anti-RBD positive at 1-month post-D3 compared to D3-mRNA (D3-JJ vs. D3-mRNA: 77% vs. 50%, $p = .022$; wIRR = ${}_{1.31}1.65_{2.08}$, $p < .001$) and at 3 month post-D3 (D3-JJ vs. D3-mRNA: 85% vs. 59%, $p = .027$; wIRR = ${}_{1.10}1.42_{1.84}$, $p = .007$). This relationship did not meet statistical significance at 6 months post-D3 (D3-JJ vs. D3-mRNA: 83% vs. 57%, $p = .11$; wIRR = ${}_{0.90}1.36_{2.03}$, $p = .14$) (Table S1a). In the smaller subset of recipient samples tested on the anti-S1 assay, there was no significant difference in anti-S1 positivity at 1-month (D3-JJ vs. D3-mRNA: 38% vs. 58%, $p = .24$; wIRR = ${}_{0.22}0.53_{1.28}$, $p = .16$) or 3 months post-D3 D3-JJ (D3-JJ vs. D3-mRNA: 70% vs. 55%, $p = .51$; wIRR = ${}_{0.73}1.20_{1.97}$, $p = .48$), though was higher in D3-JJ at 6 months post-D3 (D3-JJ vs. D3-mRNA: 100% vs. 67%, $p = .27$; wIRR = ${}_{1.05}1.45_{1.99}$, $p = .025$) (Table S1b).

3.4 | Subgroup analysis among D3-mRNA recipients

There was no difference in seropositivity post-D3 comparing the recipients of three consecutive BNT162b2 to three consecutive mRNA-1273 vaccines; 52%/51% ($p = .9$), 57%/57% ($p > .99$), and 59%/65% ($p = .8$) at 1, 3, and 6 months post-D3, respectively (Table S2). Receipt of three consecutive mRNA-1273 vaccines was associated with high-titer seroconversion at 6 month post-D3 (39% vs. 14%, $p = .029$), but this was not observed between groups at any other time point.

3.5 | Vaccine safety and adverse reactions during observation

Severe adverse reactions after D3 were rare; one D3-mRNA recipient (0.3%) reported fluid overload and a systemic inflammatory reaction temporally associated with mRNA-1273. Otherwise, the most common local adverse reaction to D3 was arm pain (D3-JJ vs. D3-mRNA: 43% vs. 69%, p .001) and the most common systemic adverse reaction was fatigue (D3-JJ vs. D3-mRNA: 48% vs. 49%, $p = .9$), followed by headache (D3-JJ vs. D3-mRNA: 38% vs. 31%, $p = .4$). No thrombotic complications, myocarditis, or anaphylactoid reactions were reported across any D3 platform (Table S3).

No D3-JJ recipients reported rejection before or after D3 during follow up. Six D3-mRNA recipients reported acute rejection during follow up, with five episodes occurred at a median 23 (12–131) days pre-D3 in two liver and three kidney recipients; none reported requiring lymphodepletion. The single post-D3 rejection episode occurred in a lung transplant recipient 68 days post-D3 and was treated with rituximab. Breakthrough COVID-19 was reported by 1 (3%) D3-JJ recipients and 35 (11%) D3-mRNA recipients ($p = .15$) at median (IQR) 139 (119, 146) days post-D3.

TABLE 2 Anti-spike seropositivity following Ad.26.COV2.S versus BNT162b2/mRNA-1273 as third dose of COVID vaccine among solid organ transplant recipients seronegative after two doses

1 month post-D3	**D3-mRNA (*n* = 269)**	**D3-JJ (*n* = 35)**	***p***
anti-S1 ≥ 1.1 or anti-RBD ≥0.8 (*n*, %)	141 (52.4%)	22 (62.9%)	0.28
anti-S1 ≥ 4 or anti-RBD ≥250 (*n*, %)	66 (24.5%)	10 (28.6%)	0.68
3 months post-D3	**D3-mRNA (*n* = 242)**	**D3-JJ (*n* = 30)**	***p***
anti-S1 ≥ 1.1 or anti-RBD ≥0.8 (*n*, %)	139 (57.4%)	24 (80.0%)	0.018
anti-S1 ≥ 4 or anti-RBD ≥250 (*n*, %)	53 (21.9%)	8 (26.7%)	0.64
6 months post-D3	**D3-mRNA (n = 76)**	**D3-JJ (*n* = 17)**	***p***
anti-S1≥1.1 or anti-RBD≥0.8 (n, %)	45 (59%)	15 (88%)	0.026
anti-S1≥4 or anti-RBD≥250 (n, %)	16 (21%)	10 (59%)	0.005

TABLE 3 Anti-spike seropositivity comparing Ad.26.COV2.S versus BNT162b2/mRNA-1273 as third dose of COVID vaccine among solid organ transplant recipients seronegative after two doses

	1-month D3-JJ: 35 D3-mRNA: 269	**3-month D3-JJ: 30 D3-mRNA: 242**	**6-month D3-JJ: 17 D3-mRNA: 76**
Standardized age (D3-JJ vs. D3-mRNA)[a]	59.5 vs. 59.7	60.0 vs. 60.1	59.1 vs. 58.8
Standardized prevalence of kidney transplant (D3-JJ vs. D3-mRNA)[a]	63% vs. 62%	65% vs. 65%	70% vs. 70%
anti-S1 ≥ 1.1 or anti-RBD ≥0.8	$_{0.98}$ 1.29 $_{1.69}$, $p = .064$	$_{1.10}$ **1.40** $_{1.77}$, $p = .006$	$_{1.04}$ **1.41** $_{1.93}$, $p = .029$
anti-S1 ≥ 4 or anti-RBD ≥250	$_{0.91}$ 1.57 $_{2.70}$, $p = .10$	$_{0.44}$ 0.92 $_{1.93}$, $p = .8$	$_{1.38}$ **2.63** $_{5.00}$, $p = .003$

Bold indicates statistically significant weighted odds ratios.

[a]After weighting procedure for imbalanced population.

4 | DISCUSSION

In this prospective cohort study of SOTRs seronegative after two-dose mRNA vaccine series, we found that recipients of Ad.26.COV2.S as heterologous D3 were more likely to be seropositive at 3- and 6 month post-D3, compared with recipients of an additional homologous mRNA vaccine. Additionally, receipt of Ad.26.COV2.S as a heterologous D3 was also associated with high-titer sero-response at 6 month post-D3. Notably, among mRNA-D3 recipients, there was no clear difference in seroconversion based upon type of vaccine received. All vaccine combinations appeared safe and well tolerated.

To some extent, our findings are consistent with the randomized trial by Reindl-Schwaighofer et al. indicating no difference in seroconversion or antibody titer at 1-month post-D3 among seronegative kidney transplant recipients receiving Ad.26.COV2.S versus mRNA vaccine.[16] However, in addition to including a larger population diverse in organs transplanted, our study extends follow up out to 3- and 6 month post-D3, revealing possible differential longer-term immunogenicity between vaccine platforms. The noted gradual rise in post-Ad.26.COV2.S immunogenicity echoes observations in the general population and is to our knowledge the first time this has been documented in the SOTR population.[17-19]

Additionally, equipoise remains about seroconversion rates and longer-term immunogenicity between receipt of BNT162b2 versus mRNA-1273 vaccines, with some suggestion of improved immune sero-response with mRNA-1273 receipt.[25,26] We did not, however, note differential seroconversion at 1, 3 and 6 month post-D3, though there was a signal particularly at 6 months for higher prevalence of high-titer sero-response in mRNA-1273 recipients. Regardless, many SOTRs remained seronegative after receiving D3-mRNA, which is consistent with historical cohorts, e.g., Benotmane et al. found that 28% of kidney transplant recipients seroconverted at 1-month after a third mRNA-1273[26] and Kamar et al. found that 44% of SOTRs seroconverted at 1-month after a third BNT162b2.[27]

This study was limited by absence of randomization, although it provided a large cohort of real-world data similar in many key demographic and transplant factors. There were some differences between D3-mRNA and D3-JJ groups including longer time interval between D2 and D3 doses in D3-mRNA recipients which might affect post-D3 sero-response, though this is less concerning as all included participants were seronegative prior to vaccination. Additionally, the D3-JJ group was older and comprised more kidney transplant recipients, factors typically associated with poorer sero-response, yet still demonstrated higher late seroconversion rates. Regarding immunogenicity assessment, formal virus neutralization was not assessed, though assays specifically associated with neutralization in the SOTR population were utilized; it is important to note that emerging data in SOTRs indicate that even persons with high-level binding may not show reliable neutralization of the Omicron variant.[28] Additionally, cellular responses were not measured, which

can show variable association with antibody level,[15,29,30] though are less well correlated with prevention of SARS-CoV-2 infection. It is possible that subclinical infections were not ascertained due to lack of anti-nucleocapsid antibody testing, which could confound antibody levels. However, participants were serially surveyed after each vaccination and twice during the January 2022 omicron wave with high response rates in order to ascertain incident COVID-19 diagnosis and/or receipt of monoclonal antibodies. Notably, all participants who did not respond to follow up surveys were mRNA-D3 recipients, which if COVID-19 ascertainment bias were present would bias the key result of higher late seroconversion in JJ-D3 toward the null.

5 | CONCLUSION

Heterologous vaccination with Ad.26.COV2.S D3 was associated with higher late seroconversion than homologous vaccination with a third mRNA dose among SOTRs negative after a 2-dose mRNA series. SOTRs with persistent negative response to mRNA vaccine series might benefit from Ad.26.COV2.S as an additional vaccine dose.

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DISCLOSURE

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AUTHOR CONTRIBUTIONS

Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: all authors. Drafting the work of revising it critically for important intellectual content: all authors. Final approval of the version to be published: TPYC, JLA, MLL, ABM, DLS, WAW. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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