Effectiveness of Monoclonal Antibody Therapy for Preventing COVID-19 Hospitalization and Mortality in a Statewide Population

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ABSTRACT

BACKGROUND: Monoclonal antibody (MAB) treatments for COVID-19 received Emergency Use Authorization in the United States.

METHODS: We used surveillance data from Rhode Island to conduct a retrospective, statewide cohort study to estimate the effectiveness of MABs for preventing hospitalization and death during periods when Alpha and Delta variants were predominant.

RESULTS: From 1/17/2021–10/26/2021, 285 long-term congregate care (LTCC) residents and 3,113 non-congregate patients met our eligibility criteria and received MAB; they were matched to 285 and 6,226 controls, respectively. Among LTCC residents, 8.8% (25/285) of patients who received MAB were hospitalized or died compared to 25.3% (72/285) of those who did not receive MAB (adjusted difference=16.7%, 95% confidence interval CI=11.0-22.3%). Among non-congregate patients, 4.5% (140/3,113) of patients who received MAB were hospitalized or died compared to 11.8% (737/6,226) of those who did not receive MAB (adjusted difference=7.2%, 95% CI=6.0-8.4%).

CONCLUSIONS: Administration of MABs led to an absolute reduction in hospitalization or death during periods when Alpha and Delta variants were predominant.

KEYWORDS: COVID-19; SARS-CoV-2; monoclonal antibody therapy; treatment effectiveness

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes Coronavirus Disease 2019 (COVID-19), is responsible for substantial morbidity and mortality across the United States (US).[1] Multiple monoclonal antibody (MAB) regimens have been granted Emergency Use Authorization (EUA) by the US Food and Drug Administration (FDA) for treatment of COVID-19[2-6] based on evidence from clinical trials suggesting a reduction in SARS-CoV-2 viral load[7-10] and hospitalization for any cause[11] after treatment. MABs are single treatments given early in the course of disease and have generally been approved for use among patients with mild to moderate symptomatic COVID-19 who were aged 12 years and older with eligible underlying conditions and/or aged 65 years and older.[2-6]

Despite evidence from the clinical trials that these MABs may help prevent medical visits, emergency department visits, and/or hospitalization for COVID-19,[7-11] evidence of their real-world effectiveness for preventing severe illness remains relatively limited, particularly for larger, population-based samples. Studies of the real-world effectiveness of MABs have similarly suggested benefits for preventing ED visits, hospitalization, intensive care unit admission, and/or death; however, all of these studies have been limited to specific integrated healthcare systems or medical centers, and most included a relatively small number of people receiving MABs.[12-17] We sought to estimate the real-world effectiveness of MAB treatment for preventing hospitalization and death among a large, statewide cohort of patients diagnosed with SARS-CoV-2 infection during periods when the Alpha (B.1.1.7 and Q lineages) and Delta (B.1.617.2 and AY lineages) SARS-CoV-2 variants were predominant.

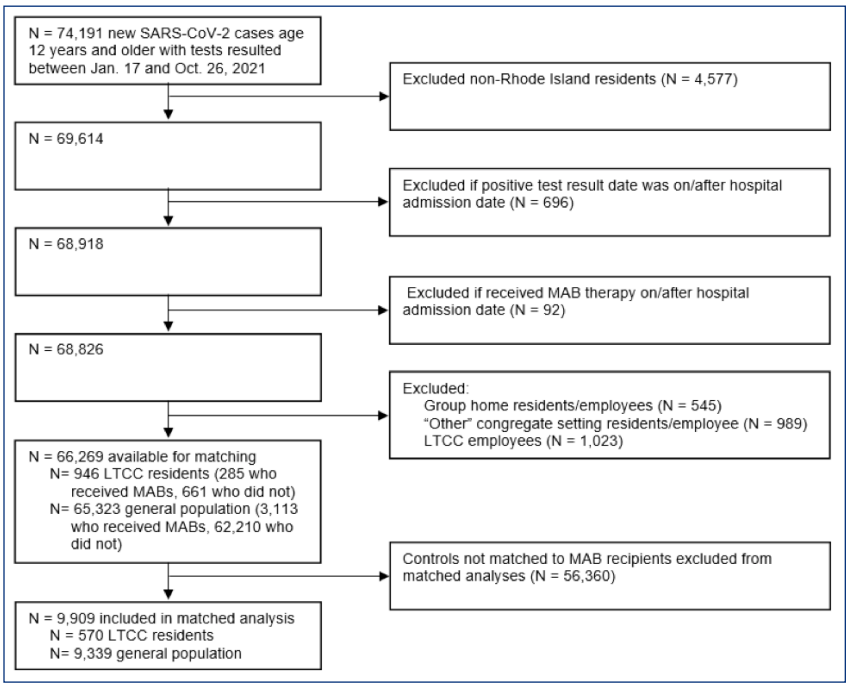
METHODS

Study design and population

We conducted a retrospective population-based cohort study using statewide surveillance data from the Rhode Island Department of Health (RIDOH) on lab-confirmed cases of SARS-CoV-2 infection among people aged 12 years and older between January 17 and October 26, 2021. Individual cases were linked to longitudinal follow-up data on MAB treatments provided for COVID-19, COVID-19 hospitalizations, and COVID-19-associated fatalities through November 11, 2021. We excluded 4,577 non-Rhode Island residents, 696 people whose first hospital admission date preceded the positive test result date, and 92 whose MAB administration came after hospitalization (**Figure 1**).

We divided our sample into two separate populations: (1) residents of long-term congregate care (LTCC) settings, which included nursing homes and assisted living facilities, and (2) patients not associated with congregate settings. LTCC residents were analyzed separately due to the high risk of morbidity and mortality in this population. We did not include group home residents or employees (n=545), "other" congregate setting residents or employees (n=989), or LTCC employees (n=1,023) in our analyses. Following

Figure 1. Application of inclusion and exclusion criteria to arrive at the final analytic sample



Abbreviations: COVID-19, Coronavirus Disease 2019; LTCC, long-term congregate care; MAB, monoclonal antibody; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

exclusions, our database included 946 LTCC residents and 65,323 residents from the general population not associated with congregate settings.

Data management and statistical methods

The study database was assembled by linking data from five surveillance systems maintained by RIDOH: SARS-CoV-2 vaccinations, cases, MAB treatments, hospitalizations, and fatalities. Linkage was done using name, date of birth, and address. In Rhode Island, vaccination data are reported to RIDOH through the Rhode Island Child and Adult Immunization Registry. Additionally, positive PCR or antigen tests are reported to RIDOH, and new cases are investigated to collect health and demographic information. Using RIDOH's statewide Hospital Incident Reporting System, hospitals report to RIDOH patients who are admitted to an inpatient bed, have recently tested (or been clinically diagnosed) positive for SARS-CoV-2 infection, and are being placed on SARS-CoV-2 precautions. RIDOH derives data for lab-confirmed COVID-19-associated fatalities from three sources: the Office of the State Medical Examiner, Vital Records death certificate data, and the Hospital Incident Reporting System. During the study period, all MAB providers in Rhode Island reported data to RIDOH on patients who were provided MAB treatments.

Our analysis was designed to estimate the average treatment effect among those treated with MAB therapy.[18] Within each stratum, we used nearest-neighbor matching based on propensity scores to match those receiving MABs to suitable controls, using a 2:1 ratio for non-congregate residents and 1:1 for LTCC residents. The propensity score model included age (years), sex assigned at birth (female, male, unknown), race/ethnicity (Hispanic or Latino, Black or African American, White, other race, unknown), symptom status (asymptomatic, symptomatic, not interviewed, unknown), timing of positive test result (number of days since January 17, 2021), and vaccination status at time of the positive test result (completed primary vaccination series, partially completed primary vaccination series, unvaccinated). For the non-congregate sample, we also included a ZIP-code-based 3-tier community risk classification created by RIDOH to help guide COVID-19 surveillance and response efforts (low-, moderate-, and high-risk tiers). The tier classification was based on community characteristics such as population density, sociodemographics, and COVID-19 burden.

For each matched sample, we estimated the difference in the percentage who were hospitalized or died (i.e., a combined outcome) between those receiving and not receiving MAB therapy. We also fit a regression model adjusted for the covariates used in matching to correct for potential post-matching imbalances. The estimated difference from these models corresponds to the average increase in hospitalization or death, among those who received MABs, that would have been realized had they not received MAB treatment. In other words, the effect estimates apply to the subset of the population who actually received MABs.

Although we used a combined outcome to improve efficiency for our primary analysis, we also fit a multinomial logistic regression model with the two outcomes modeled separately (hospitalization only, death) to determine whether the results were driven by one outcome. Finally, to understand the potential influence of cases who received MABs later in the course of their COVID-19 infection, we conducted a sensitivity analysis restricted to people who received MABs within five days of their positive test result date and their matched controls.

This study was classified as exempt by the RIDOH Institutional Review Board. We utilized SAS 9.4 (Cary, North Carolina) and Python 3.8.5 (Wilmington, Delaware) for data management and Stata 17 (College Station, Texas) for statistical analyses. Counts of less than five are suppressed in accordance with RIDOH's Small Numbers Policy. (Additional detail on the data systems, definitions, data sources, and linkage methods is available in a supplementary appendix by emailing corresponding author.)

RESULTS

A total of 3,398 patients received MABs and were included in our analyses. This included 285 of 946 LTCC residents and 3,113 of 65,323 non-congregate setting patients who received MABs (1,234 bamlanivimab monotherapy, 639 bamlanivimab and etesevimab, and 1,514 casirivimab and imdevimab, 9 sotrovimab, and <5 unknown). Within each subsample, we used propensity scores to match MAB recipients to controls (1:1 for LTCC and 1:2 for general population). Our analysis datasets were based on 570 LTCC residents (285 MAB recipients and 285 matched controls) and 9,339 individuals not in a congregate setting (3,113 MAB recipients and 6,226 matched controls).

Sociodemographic and health characteristics of the matched samples are shown in Tables 1 and 2 and indicate that the samples are well balanced on these covariates. The sample of MAB recipients among LTCC residents had average age 80.4 years (standard deviation SD 12.2), was 57.2% female, with 26.7% confirmed symptomatic (42.1% had unknown symptom status) and 41.0% unvaccinated; race/ethnicity was unknown for 80.3%. In this sample of LTCC residents who received MABs, mean number of days from January 17, 2021, to positive SARS-CoV-2 test was 105.1 days (SD 105.7) (**Table 1**). For MAB recipients not in congregate settings, mean age was 58.7 years (SD 15.5); 53.6% were female, 77.9% were white, 86.3% were confirmed symptomatic, and 67.5% were unvaccinated. In this sample of MAB recipients not associated with congregate settings, timing of positive test relative to January 17, 2021, was 148.0 days (SD 103.0). Residents of moderate- or high-risk communities, per RIDOH's ZIP-code-based community COVID-19 risk classification, comprised 42.8% of the non-congregate sample (**Table 2**).

In the matched sample, 25 of 285 (8.8%) LTCC resident patients who received MABs were hospitalized only (n=9) or died (n=16) with COVID-19 compared to 72 of the 285 (25.3%) who did not receive MABs (n=42 hospitalized only, n=30 died); the adjusted risk difference for the combined outcome of hospitalization or death was 16.7% (95% CI 11.0 to 22.3%) (**Table 3**). Among non-congregate setting residents, hospitalization or death occurred for 140 of 3,113 MAB recipients (4.5%; n=131 hospitalized only, n=9 died) and 737 of 6,226 who did not receive MABs (11.8%; n=599 hospitalized only, n=138 died), with adjusted risk difference 7.2% (95% CI 6.0 to 8.4%).

When modeling hospitalization only and death separately to determine whether the results were driven by one outcome, MABs were protective against both hospitalization only and death for LTCC residents and the general population (**Table 4**). Importantly, death was a more frequent outcome for LTCC residents than non-congregate patients. Among LTCC residents, there was some evidence that the relative impact of MABs was greater for preventing hospitalization only than death. Conversely, among non-congregate patients, the relative impact of MABs was somewhat greater for preventing death than hospitalization only.

Finally, in our sensitivity analysis restricted to cases who received MABs within five days of their positive test result date and their matched controls, the results were similar (supplementary appendix Table S1 available by emailing corresponding author).

Table 1. Summary of matching covariates for the matched sample of LTCC resident patients

Characteristic	MAB N=285 n (%)	No MAB N=285 n (%)	Standardized difference
Age (years), mean (SD)	80.35 (12.2)	79.70 (12.1)	0.054
Days since 1/17/21, mean (SD)	105.1 (105.7)	113.3 (103.2)	-0.077
Sex			
Female	163 (57.2)	166 (58.3)	-0.021
Male	75 (26.3)	67 (23.5)	0.063
Unknown	47 (16.5)	52 (18.2)	-0.047
Race/ethnicity			
White*	49 (17.2)	49 (17.2)	0.000
Hispanic or Latino	<5†	<5†	†
Other race*	5 (1.8)	<5†	†
Unknown	229 (80.3)	228 (80.0)	0.009
Symptom status‡			
Asymptomatic	87 (30.5)	87 (30.5)	0.000
Symptomatic	76 (26.7)	77 (27.0)	-0.008
Not Interviewed	<5†	<5†	†
Unknown	120 (42.1)	119 (41.8)	0.007
Vaccination status			
Completed primary vaccination series	98 (34.4)	101 (35.4)	-0.022
Partially completed primary vaccination series	70 (24.6)	62 (21.8)	0.065
Unvaccinated	117 (41.0)	122 (42.8)	-0.036
Community COVID-19 risk§			
High	26 (9.1)	27 (9.5)	-0.012
Moderate	43 (15.1)	45 (15.8)	-0.020
Low	208 (73.0)	202 (70.9)	0.047
Unknown	8 (2.8)	11 (3.8)	-0.064

Abbreviations: COVID-19, Coronavirus Disease 2019; LTCC, long-term congregate care; MAB, monoclonal antibody; RIDOH, Rhode Island Department of Health; SD, standard deviation.

* Patient reported non-Hispanic or unknown ethnicity.

† Counts of 1-4 and calculations based on those counts are suppressed, in accordance with RIDOH's Small Numbers Policy.

‡ Summary of symptom information reported to RIDOH as the reason for testing, during case investigation, and/or through symptom self-monitoring. Congregate setting residents often are not interviewed for symptom information.

§ ZIP-code-based community risk classification created by RIDOH based on community characteristics such as population density, sociodemographics, and COVID-19 burden to help guide COVID-19 surveillance and response efforts.

Table 2. Summary of matching covariates for the matched sample of patients not associated with a congregate setting

Characteristic	MAB N=3,113 n (%)	No MAB N=6,226 n (%)	Standardized difference
Age (years), mean (SD)	58.7 (15.5)	58.8 (16.0)	-0.006
Days since 1/17/21, mean (SD)	148.0 (103.0)	145.0 (97.4)	0.028
Sex			
Female	1,667 (53.6)	3,250 (52.2)	0.027
Male	1,324 (42.5)	2,757 (44.3)	-0.035
Unknown	122 (3.9)	219 (3.5)	0.021
Race/ethnicity			
Hispanic or Latino (any race)	360 (11.6)	691 (11.1)	0.015
Black or African American*	105 (3.3)	216 (3.5)	-0.005
White*	2,425 (77.9)	4,914 (78.9)	-0.025
Other race*	103 (3.3)	170 (2.7)	0.032
Unknown	120 (3.9)	235 (3.8)	0.004
Symptom status‡			
Asymptomatic	119 (3.8)	222 (3.6)	0.013
Symptomatic	2,685 (86.3)	5,362 (86.1)	0.004
Not Interviewed	308 (9.9)	640 (10.3)	-0.013
Unknown	<5†	<5†	†
Vaccination status			
Completed primary vaccination series	879 (28.2)	1638 (26.3)	0.043
Partially completed primary vaccination series	134 (4.3)	254 (4.1)	0.011
Unvaccinated	2,100 (67.5)	4,334 (69.6)	-0.046
Community COVID-19 risk§			
High	471 (15.1)	916 (14.7)	0.012
Moderate	861 (27.7)	1654 (26.6)	0.024
Low	1,765 (56.7)	3,623 (58.2)	-0.030
Unknown	16 (0.51)	33 (0.53)	-0.002

Abbreviations: COVID-19, Coronavirus Disease 2019; MAB, monoclonal antibody; RIDOH, Rhode Island Department of Health; SD, standard deviation.

* Patient reported non-Hispanic or unknown ethnicity.

† Counts of 1-4 and calculations based on those counts are suppressed, in accordance with RIDOH's Small Numbers Policy.

‡ Summary of symptom information reported to RIDOH as the reason for testing, during case investigation, and/or through symptom self-monitoring.

§ ZIP-code-based community risk classification created by RIDOH based on community characteristics such as population density, sociodemographics, and COVID-19 burden to help guide COVID-19 surveillance and response efforts.

Table 3. Number and percentage who were hospitalized only or died with COVID-19 by MAB treatment status, among matched samples (combined outcome)

	MAB n (%)	No MAB n (%)	Unadjusted difference (95% CI)	Adjusted difference (95% CI)
LTCC residents	25/285 (8.8%)	72/285 (25.3%)	16.5% (10.4–22.5%)	16.7% (11.0–22.3%)
Hospitalized only	9	42		
Died	16	30		
Non-congregate setting patients	140/3,113 (4.5%)	737/6,226 (11.8%)	7.3% (6.1–8.6%)	7.2% (6.0–8.4%)
Hospitalized only	131	599		
Died	9	138		

Abbreviations: CI, confidence interval; COVID-19, Coronavirus Disease 2019; LTCC, long-term congregate care; MAB, monoclonal antibody.

Table 4. Number and percentage who were hospitalized only or died with COVID-19 by MAB treatment status, among matched samples (separate outcomes)

	MAB n (%)	No MAB n (%)	Unadjusted relative risk ratio (95% CI)*	Adjusted relative risk ratio (95% CI)*
LTCC residents				
Hospitalized only	9/285 (3.2%)	42/285 (14.7%)	0.18 (0.08–0.37)	0.17 (0.08–0.36)
Died	16/285 (5.6%)	30/285 (10.5%)	0.44 (0.23–0.82)	0.42 (0.22–0.80)
Non-congregate setting patients				
Hospitalized only	131/3,113 (4.2%)	599/6,226 (9.6%)	0.40 (0.33–0.49)	0.39 (0.32–0.48)
Died	9/3,113 (0.3%)	138/6,226 (2.2%)	0.12 (0.06–0.24)	0.12 (0.06–0.24)

Abbreviations: CI, confidence interval; COVID-19, Coronavirus Disease 2019; LTCC, long-term congregate care; MAB, monoclonal antibody.

* Relative risk ratio (RRR) for the effect of receiving MABs. For example, if Ω_H is the relative risk of hospitalization (risk among those receiving MABs divided by risk among those not) and Ω_N is the relative risk of no adverse outcome, then Ω_H = (RRR)* Ω_N. Hence, as RRR decreases, so does the risk of hospitalization for those who receive MAB. The same reasoning holds for the mortality endpoint.

DISCUSSION

This was among the first population-based studies to evaluate the real-world effectiveness of MAB treatment for mild-to-moderate COVID-19 for preventing severe illness. In statewide, population-based samples matched on age, sex, race/ethnicity, symptom status, vaccination status, community COVID-19 risk, and timing of positive SARS-CoV-2 test relative to January 17, 2021, we found that the effect of MABs among those who received it was to reduce probability of hospitalization or death from 25.3% to 8.8% for residents of LTCC residents and from 11.8% to 4.5% for non-congregate settings patients, during periods when the Alpha and Delta strains of SARS-CoV-2 were predominant. The overall rates of hospitalization and mortality were higher than for the general population because the subpopulation who receives MABs, which was the focus of this analysis, is at much higher risk for these outcomes.

Our large, statewide study suggests that, prior to the emergence of the Omicron variant (B.1.1.529, BA.1, BA.1.1, BA.2, BA.3, BA.4, and BA.5 lineages), MABs were effective for preventing hospitalization and death in the context of real-word utilization. This finding is generally consistent with prior studies of real-world MAB use for preventing emergency department visits, hospitalization, intensive care unit admission, and/or mortality among patients of specific integrated health care systems or medical centers.[12-17] Although overall MAB utilization in our study was relatively low (30.1% among LTCC residents, 4.7% among non-congregate setting patients), this generally makes sense given the EUA criteria for MAB treatment, which generally required patients to be symptomatic (all ages) and have qualifying underlying conditions (ages 12–64 years).[2-5] We accounted for differences in underlying risk of hospitalization or death between patients who did and did not receive MABs by propensity score matching on available sociodemographic and clinical characteristics and time. We were not able to match on unmeasured factors that may have impacted likelihood of receiving MABs and risk of severe illness, such as key comorbidities that were required for younger people to receive MABs under the EUAs[2-5] and other social and structural factors that may influence access to MABs and health outcomes. Although the supply of MABs was limited during portions of the study period, we included the timing of patients' positive test results in our propensity score matching, which should help to account for temporal trends in MAB availability. Importantly, our results suggest that MABs were effective among both LTCC residents and non-congregate setting patients; however, the average age of non-congregate setting patients who received MABs in our study was about 60 years. Although we included younger patients who received MABs, additional research on the effectiveness of MABs specifically among eligible young patients would be useful.

Our study was conducted during a period where Rhode Island, like the rest of the United States, was experiencing the rapid emergence of multiple SARS-CoV-2 variants of concern or interest. For roughly the first half of the study period, the largest number of variants of concern detected in Rhode Island were Alpha 19, which has been found to be susceptible in-vitro to the four MAB regimens utilized during the study period.[2-5] The Delta variant emerged rapidly during the second half of our study period[19] and has reduced susceptibility to bamlanivimab monotherapy[20] (which was no longer in use in Rhode Island after April 2021)[21] and bamlanivimab/etesevimab[3], while susceptibility to casirivimab/imdevimab and sotrovimab were unchanged.[4, 5] Importantly, MAB effectiveness is expected to vary over time and by geography, depending on the SARS-CoV-2 strains in circulation and the MAB regimens utilized. In particular, although it was not in circulation during our analysis period, in-vitro studies suggest that the Omicron variant has reduced susceptibility to the MABs that were available during the study period,[3-5] and recently emerging Omicron sub-variants may have reduced susceptibility to a newer MAB that was granted EUA following the study period,[6] highlighting the need to reformulate, test, and manufacture MABs rapidly in response to circulating SARS-CoV-2 strains.

Our report has limitations. First, as mentioned above, we did not have full information on certain comorbidities required for MAB eligibility among young people under the EUAs [2-4] and associated with increased risk of hospitalization or death. Although we aimed to account for differences between patients who did and did not receive MABs using propensity score matching, our results may be subject to residual confounding by indication. Second, our MAB and hospitalization data systems only collected data from providers and hospitals in Rhode Island. Thus, we may be missing MAB treatment data and/or hospitalization data for Rhode Island residents treated or hospitalized out of state; however, this constraint is not likely to contribute systematically to bias in estimation of treatment effect. (In our manual review of notes from a subset of calls about MABs to patients who live in cities/towns bordering Massachusetts and Connecticut, we did not identify patients voicing their intention to receive MABs out of state. Additionally, of all deaths among Rhode Island residents, only 0.2% are known to have occurred out of state, which may suggest that a relatively small percentage of Rhode Islanders with severe illness were hospitalized out of state.) Third, the limited sample size of patients receiving MABs prevented us from stratifying our analysis by MAB drug type and time-period. As additional data are accrued, a follow-up stratified analysis would be useful. Fourth, data on symptom status are limited to the information reported to RIDOH as the reason for testing, during case investigation, and/or through symptom self-monitoring and may be incomplete. Finally, we required at least two weeks of follow-up time for assessment of hospitalization and fatality outcomes based on the usual time

between the positive SARS-CoV-2 test result date and hospital admission and death with COVID-19 in Rhode Island. Nonetheless, for patients diagnosed with SARS-CoV-2 at the end of our study period (e.g., late October 2021), we may be missing some delayed outcomes that occurred after November 11, 2021.

In conclusion, our analysis provides evidence that, prior to the emergence of the Omicron variant, MABs were an effective tool for preventing hospitalization and death among patients with mild to moderate COVID-19. Our analysis supports the idea that state and local health jurisdictions, health care systems, LTCC facilities, and individual health care providers strengthen efforts to make MABs with activity against currently circulating variants readily available and easy-to-access, even in the context of widespread SARS-CoV-2 vaccination, given challenges rapidly achieving herd immunity in all populations. Future research on real-world MAB effectiveness by drug type, time-period, and SARS-CoV-2 strain, as well as among young people with underlying conditions, would be useful to inform our understanding of which patients are most likely to benefit from MAB treatment over time.

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Disclosures

All authors declare that they have no conflicts of interest. The views expressed herein are those of the authors and do not necessarily reflect the views of the Rhode Island Department of Health or Brown University.

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