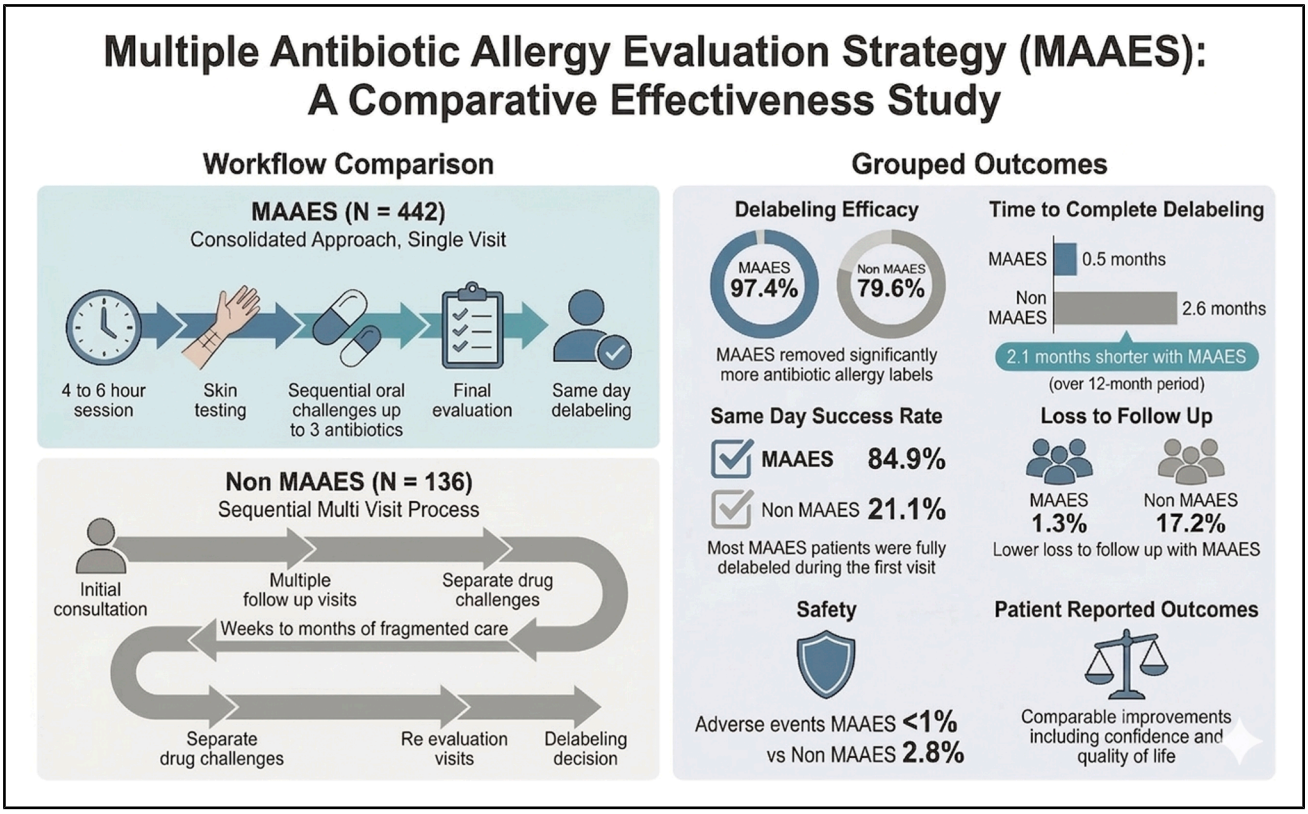
Original Article

Multiple Antibiotic Allergy Evaluation Strategy (MAAES): A Comparative Effectiveness Study

Thanaporn Ratchataswan, MD, Rebecca Lee, MPH, Amir Asiaee, PhD, Matthew S. Krantz, MD, Grace Koo, MD, Cosby A. StoneJr. MD, MPH, et al

VISUAL SUMMARY



What is already known about this topic? Antibiotic allergy labels are common but frequently inaccurate. Patients with multiple labels often require sequential evaluations across multiple visits, delaying delabeling, increasing loss to follow-up, and limiting access to first-line antibiotics.

What does this article add to our knowledge? A consolidated Multiple Antibiotic Allergy Evaluation Strategy (MAAES) improves delabeling success, accelerates complete delabeling, and reduces loss to follow-up while maintaining safety and providing similar patient-reported outcomes compared with traditional sequential evaluation.

How does this study impact current management guidelines? These findings support consideration of MAAES as a safe and effective approach to accelerate and streamline evaluation and delabeling in patients with multiple low-risk antibiotic allergy labels.

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Multiple Antibiotic Allergy Evaluation Strategy (MAAES): A Comparative Effectiveness Study

Thanaporn Ratchataswan, MD[a], Rebecca Lee, MPH[b], Amir Asiaee, PhD[c], Matthew S. Krantz, MD[a], Grace Koo, MD[a], Cosby A. Stone, Jr., MD, MPH[a], and Elizabeth J. Phillips, MD[b,d,e] *Nashville, Tenn; and Murdoch, WA, Australia*

BACKGROUND: Inaccurate multiple antibiotic allergy labels to first-line agents (penicillins, cephalosporins, and sulfonamides) restrict optimal therapy and often require sequential evaluations across multiple visits, delaying delabeling and increasing loss to follow-up.

OBJECTIVE: To conduct a comparative effectiveness study of the Multiple Antibiotic Allergy Evaluation Strategy (MAAES), comparing its effectiveness, safety, and patient-reported outcomes (PRO) with traditional sequential evaluation (non-MAAES).

METHODS: This retrospective cohort study (2014-2024) compared same-day multi-antibiotic testing (MAAES) with non-MAAES in patients with 2 or more low-risk labels. Multivariable regression adjusted for baseline differences and testing era. Inverse probability of treatment weighting (IPTW) and a restricted post-2020 subcohort analysis addressed selection bias and temporal shifts. Outcomes included delabeling efficacy, time to complete delabeling, loss to follow-up, relabeling, adverse events (AEs), and PRO.

RESULTS: Baseline differences were present between the MAAES and non-MAAES groups, including penicillin anaphylaxis (1.4% vs 6.6%, $P = .002$), angioedema (12.4% vs 19.1%, $P = .049$), maculopapular rash (13.1% vs 24.3%, $P = .002$), and unknown sulfonamide history (9.5% vs 3.7%, $P = .03$). MAAES removed 97.4% of labels versus 79.6% for non-MAAES (adjusted odds ratio [aOR]: 9.41, 95% confidence interval [CI]: 5.22-16.95, $P < .001$). MAAES achieved faster complete delabeling (log-rank $\chi^2 = 42.4$, $P < .001$), with 84.9% versus 21.1% delabeled at the initial visit (restricted mean survival time difference: 2.1 months). Results remained robust in post-2020 and IPTW models. Loss to follow-up (1.3% vs 17.2%; aOR: 0.06, 95% CI: 0.03-0.13, $P < .001$) and AEs (<1% vs 2.8%; aOR: 0.26, 95% CI: 0.09-0.78, $P = .02$) were significantly lower with MAAES. Favorable PRO was sustained, with no significant differences between groups.

CONCLUSIONS: A consolidated multidrug evaluation strategy substantially improves the effectiveness of first-line antibiotic allergy delabeling while maintaining excellent safety profiles and PRO. **(J Allergy Clin Immunol Pract 2026;■:■-■)**

Key words: *Antibiotic allergy label; Multiple drug allergy; Beta-lactam allergy; Sulfonamide allergy; Penicillin allergy; Cephalosporin allergy; Drug allergy delabeling; Drug hypersensitivity; Antimicrobial stewardship*

INTRODUCTION

Antibiotic allergy labels (AAL) to first-line agents, including penicillins (PAL), cephalosporins (CAL), and sulfonamides (SAL), are common yet frequently unverified. Over 95% lack true hypersensitivity.[1,2] Beyond individual drug labels, multiple drug allergy or intolerance labels are reported in 1.2% to 6.4% of patients.[3] Many AAL can be removed through appropriate evaluation and testing.[4-6] Inaccurate labels drive the use of broad-spectrum alternatives, increasing costs, antimicrobial resistance, and adverse clinical outcomes.[7-10]

Although delabeling programs are established stewardship tools supported by guidelines,[11-15] managing multiple AAL is complex and access to comprehensive drug allergy evaluation remains limited. Such patients often experience fragmented care requiring multiple visits, causing delays, increased costs, and decreased adherence. We previously demonstrated that single-

[a]Division of Allergy, Pulmonary, and Critical Care Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tenn
[b]Division of Infectious Diseases, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tenn
[c]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, Tenn
[d]Department of Pathology, Microbiology, and Immunology, Vanderbilt University School of Medicine, Nashville, Tenn
[e]Institute for Immunology and Infectious Diseases, Murdoch University, Murdoch, WA, Australia

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Corresponding author: Elizabeth J. Phillips, MD, Vanderbilt University Medical Center, 1161 21st Ave South, A-2200, Medical Center North, Nashville, TN 37232. E-mail: elizabeth.j.phillips@vumc.org.

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Abbreviations used
AAL- Antibiotic allergy label
AE- Adverse event
aOR- Adjusted odds ratio
CAL- Cephalosporin allergy label
EHR- Electronic health record
IPTW- Inverse probability of treatment weighting
MAAES- Multiple Antibiotic Allergy Evaluation Strategy
MD- Mean difference
OR- Odds ratio
PAL- Penicillin allergy label
PRO- Patient-reported outcome
RMST- Restricted mean survival time
SAL- Sulfonamide allergy label
TMP-SMX- Trimethoprim-sulfamethoxazole

visit multiallergy evaluation is feasible, though 25% were relabeled within 1 year.[16] To address these barriers, the Vanderbilt Drug Allergy Clinic implemented the Multiple Antibiotic Allergy Evaluation Strategy (MAAES) in 2014. Although feasibility and safety have been demonstrated in solid organ transplant populations,[17] comparative effectiveness data in broader outpatient populations are unknown. This 10-year study is the first to compare the efficacy, safety, and patient-reported outcomes (PRO) of the MAAES protocol against non-MAAES care in a general outpatient population.

METHODS

Retrospective cohort design

We conducted a retrospective cohort study approved by the Vanderbilt University Medical Center Institutional Review Board (#161455), evaluating patients with 2 or more low-risk AAL (PAL, CAL, or SAL) seen at the Vanderbilt Drug Allergy Clinic between March 2014 and April 2024. Data were managed via REDCap to track demographics, testing timelines, and clinical outcomes. Patients were categorized into 2 groups: MAAES (consolidated same-day testing of $\geq$2 labels) or non-MAAES (traditional sequential evaluation across multiple visits). Risk assessment followed a 3-tier process: electronic health record (EHR) review, clinician-led history reconciliation, and guideline-based stratification.[5,6,13,14,18] Remote unknown reaction histories were categorized as low-risk and allocated to either the MAAES or the traditional pathway based on shared decision-making.

Patients were excluded from low-risk classification if they reported anaphylaxis within the past 5 years; immediate reactions within 1 hour, including diffuse urticaria, angioedema, respiratory symptoms, hypotension, syncope, or gastrointestinal symptoms; or delayed urticarial eruptions within the past 5 years. Patients were also excluded for severe cutaneous or systemic reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, immune-mediated kidney or liver injury, or delayed skin or mucosal sloughing or ulceration. Allergy labels to intravenous cephalosporins were excluded because of a higher pretest probability of true allergy and ineligibility for direct oral challenge delabeling.[6]

MAAES protocol

The MAAES protocol targets remote, low-risk AAL using a single-visit approach involving indicated skin testing and up to 3 sequential oral challenges (Figure 1). Penicillin and cephalosporin skin testing is performed for higher-risk histories per established protocols,[4,6] whereas trimethoprim-sulfamethoxazole (TMP-SMX) undergoes 1- or 2-step direct challenges, as skin testing has limited predictive value.[5] Sequential same-day challenges enable multi-antibiotic evaluation during a single 4- to 6-hour visit. Without a fixed washout period, the next agent is administered if the patient remains asymptomatic after a 90-minute (penicillins/cephalosporins) or 120-minute (TMP-SMX) observation. Since 2020, selected low-risk reactions have been evaluated with direct oral challenges without prior skin testing.[5,6,13,14] Patients are monitored every 30 minutes during testing and contacted 24 hours after evaluation (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). Drug attribution was determined by symptom onset relative to the 90- to 120-minute interchallenge observation window. Immediate reactions were attributed to the most recent agent, while rare delayed reactions were assigned based on drug-specific risk profiles, specifically sulfonamides prioritized over beta-lactams. Ambiguous cases were resolved via single-agent rechallenge of the least suspected drug. After successful delabeling, discharge summaries are shared with patients, providers, and pharmacies to ensure clinical loop-closure.

Outcomes

Primary outcomes included 3 domains: (1) delabeling efficacy, defined as the proportion of AAL removed relative to baseline AAL and time to complete delabeling; (2) delabeling effectiveness, defined by loss to follow-up and relabeling rates per label tested; and (3) safety, defined as documented adverse events (AEs) related to allergy testing or drug challenge.

Complete delabeling was defined as removal of all documented AAL ($\geq$2 labels to none), and the time to complete delabeling was calculated from the initial evaluation to the date all labels were removed. Patients with $\geq$1 AAL remaining were excluded from this analysis. Loss to follow-up was defined as failure to complete the planned evaluation for a specific drug such as skin testing without returning for oral challenge. Relabeling was defined as re-entry of a previously removed allergy into the EHR by any source.

Survey design and PRO

A cross-sectional survey was distributed via REDCap to 343 patients through email and electronic health portals, as electronic contact information was unavailable for some patients. The questionnaire assessed PRO using Likert-type scales and free-text items. Measured domains included satisfaction, confidence in allergy status, medication use post-delabeling, anxiety, quality of life (emotional, physical, and social), health care expenses, and trust in providers.

Statistical analysis

Data were analyzed using R version 4.3 and SPSS version 23.0. Continuous variables were compared using Wilcoxon rank-sum tests, and categorical variables were compared using Pearson χ^2 or Fisher exact tests.

Primary outcomes

Outcomes were evaluated using unadjusted and multivariable models to control for potential confounding. These models were adjusted for 5 prespecified covariates: history of penicillin anaphylaxis, angioedema, maculopapular rash, unknown sulfonamide reaction history, and testing era (post-2020 vs earlier). Outcomes were analyzed at 2 levels to account for the complexity of multiple

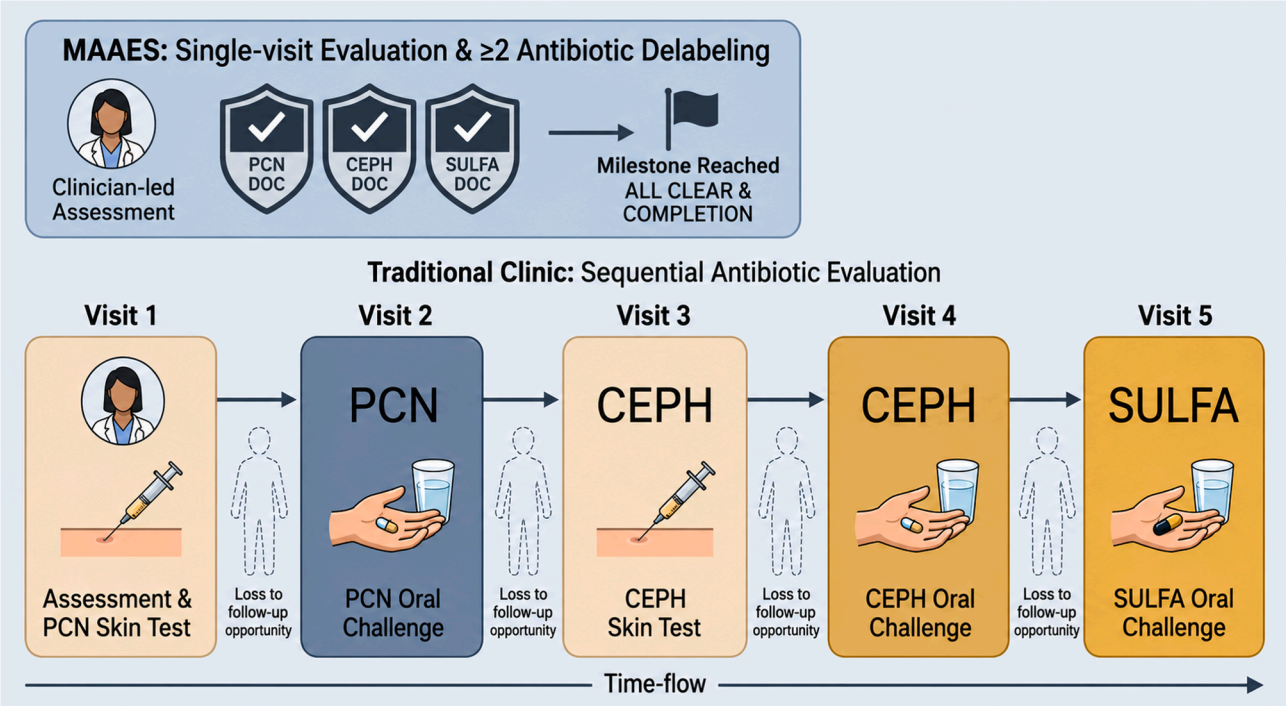

FIGURE 1. Comparison between Multiple Antibiotic Allergy Evaluation Strategy (MAAES) and other sequential testing strategies. Scenario: a patient has 3 first-line antibiotic allergy labels. *CEPH*, Cephalosporins; *DOC*, direct oral challenge; *PCN*, penicillin; *SULFA*, sulfonamide.

allergies per individual. Patient-level outcomes, including successful delabeling of all antibiotic combinations and the total number of labels removed per patient, were modeled using logistic regression and ordinary least squares, respectively. Label-level outcomes, including the delabeling of specific AAL, failed challenges, relabeling, and AEs, were modeled using logistic regression with patient-clustered Huber-White standard errors to account for intrapatient correlation. Multiplicity was addressed using Holm and Benjamini-Hochberg adjusted *P* values. The multiplicity family comprised the 4 label-level outcomes (loss to follow-up, failed challenge, relabeling, and any AEs); *P* values reported in the tables are nominal.

Time-to-event analysis

Time to complete delabeling was evaluated using Kaplan-Meier curves and the log-rank test. Because proportional-hazards assumption was violated (Schoenfeld residual test $P < .001$), restricted mean survival time (RMST) with a 12-month horizon was used to quantify the average difference in time to delabeling. Same-day delabeling rates were further compared using multivariable logistic regression.

Sensitivity and bias adjustment

To address potential selection bias and temporal confounding, a propensity-score sensitivity analysis was conducted. The propensity to receive MAAES was estimated using a logistic regression model incorporating the 5 prespecified covariates plus baseline allergy-label count. Stabilized inverse probability of treatment weighting (IPTW) was applied to a quasibinomial logistic regression for primary delabeling and to RMST for time to delabeling. Covariate balance was confirmed using an absolute standardized mean difference (MD) threshold of <0.10. A nearest-neighbor caliper matching analysis was also performed as a robustness check. Finally, analyses were repeated, restricted to the post-2020 subcohort to account for the clinical shift toward direct oral challenges.

PRO analysis

Changes in PRO were analyzed using a cumulative link mixed model pooling all domains, with a random intercept for the patient. Models compared pathways adjusting for total number of visits and history of penicillin-associated angioedema, as these factors differed significantly between groups, and for time from testing to survey completion to account for recall bias. A likelihood ratio test assessed whether pathway effects differed across domains. Sensitivity analyses included binary improvement rates, Wilcoxon rank-sum tests for ordinal scores, and analysis of a composite PRO score (mean change across domains on a −2 to +2 scale). Worsening, defined as any negative change from baseline, was compared using Fisher exact tests. Significance was set at $P < .05$.

RESULTS

Cohort characteristics

Between March 1, 2014, and April 30, 2024, a total of 803 patients were evaluated in the Vanderbilt Drug Allergy Clinic. Of these, 578 (72%) met the inclusion criteria (≥2 low-risk penicillin, cephalosporin, or TMP-SMX labels). The remaining 225 (28%) were excluded because of high-risk reaction histories. The MAAES group comprised 442 patients (76.5%; 919 labels), while 136 (23.5%; 285 labels) underwent traditional sequential evaluation. Most patients were female (83.4%) and self-reported their race as White (84.8%) (Table I), with a median of 2 labels (interquartile range: 2-2) in both groups.

TABLE I. Baseline characteristics and antibiotic allergy label distribution

Characteristic	MAAES (n = 442)	Non-MAAES (n = 136)
Age (y), median (IQR)	59.8 (44.4-70.3)	62.8 (47.3-69.7)
Sex: female	370 (83.7)	112 (82.4)
Self-reported race		
White	375 (84.8)	115 (84.6)
African American	17 (3.8)	8 (5.9)
American Indian/Alaska Native	2 (0.5)	1 (0.7)
Asian	2 (0.5)	0 (0)
Native Hawaiian/Other Pacific Islander	0 (0)	0 (0)
Others	0 (0)	1 (0.7)
Unknown	46 (10.4)	11 (8.1)
Ethnicity		
Hispanic or Latino	9 (2.0)	1 (0.8)
Not Hispanic or Latino	370 (83.7)	117 (86.0)
Unknown	63 (14.3)	18 (13.2)
In-state residence	374 (84.6)	117 (86.0)
Distribution of antibiotic allergy label combinations		
PAL+CAL	185 (41.9)	71 (52.2)
PAL+SAL	169 (38.2)	43 (31.6)
CAL+SAL	54 (12.2)	9 (6.6)
PAL+CAL+SAL	34 (7.7)	13 (9.6)
Medical comorbidities		
Hypertension	198 (44.8)	70 (51.5)
Asthma/COPD	120 (27.2)	39 (28.7)
Depression	103 (23.3)	30 (22.1)
Anxiety disorder	91 (20.6)	22 (16.2)
Bipolar disorder	6 (1.4)	2 (1.5)
Diabetes	80 (18.1)	21 (15.4)
Malignancy	98 (22.2)	35 (25.7)
Autoimmune disease	79 (17.9)	24 (17.6)
Transplant recipient	30 (6.8)	4 (2.9)
Urticaria/angioedema	16 (3.6)	7 (5.1)
Cystic fibrosis	3 (0.7)	1 (0.7)
Primary immune deficiency	18 (4.1)	5 (3.7)
HIV	9 (2.0)	3 (2.2)
Dementia	2 (0.5)	2 (1.5)
Mast cell disorder	4 (0.9)	1 (0.7)

Data are presented as n (%) unless otherwise specified.
CAL, Cephalosporin allergy labels; *COPD*, chronic obstructive pulmonary disease; *HIV*, human immunodeficiency virus; *IQR*, interquartile range; *MAAES*, Multiple Antibiotic Allergy Evaluation Strategy; *PAL*, penicillin allergy labels; *SAL*, sulfonamide allergy labels.

Fifteen percent lived out of state. Comorbidities and the distribution of allergy label combinations (PAL+CAL, PAL+SAL, CAL+SAL, and PAL+CAL+SAL) did not differ between groups ($P = .07$) (Table I). In the MAAES group, 418 of 919 (45.5%) labels underwent a direct oral challenge, and 501 (54.5%) underwent skin testing followed by an oral challenge. In the non-MAAES group, 75 of 285 (26.3%) underwent a direct oral challenge, 143 (50.2%) underwent skin testing with an oral challenge, and 67 (23.5%) underwent skin testing alone (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

TABLE II. Variables differing between MAAES and non-MAAES

Variable	MAAES (n = 442)	Non-MAAES (n = 136)	*P* value
History of anaphylaxis to penicillin	6 (1.4)	9 (6.6)	.002
History of angioedema to penicillin	55 (12.4)	26 (19.1)	.049
History of maculopapular rash to penicillin	58 (13.1)	33 (24.3)	.002
Unknown history of sulfonamide	42 (9.5)	5 (3.7)	.03

Data are presented as n (%).
MAAES, Multiple Antibiotic Allergy Evaluation Strategy.

When examining variables associated with pathway selection, patients in the non-MAAES group had a higher prevalence of prior higher-risk penicillin histories, including anaphylaxis and angioedema, and also more frequently reported maculopapular rash. In contrast, an unknown sulfonamide history was more common in the MAAES group (Table II).

Primary outcome

Delabeling efficacy. Of 919 labels in the MAAES group, 895 (97.4%) were ultimately removed versus 227 of 285 (79.6%) in the non-MAAES group (odds ratio [OR]: 9.53, 95% confidence interval [CI]: 5.40-16.83, $P < .001$). After adjustment for the 5 prespecified covariates, the OR attenuated only marginally to 9.41 (95% CI: 5.22-16.95, $P < .001$). At the patient level, the MAAES strategy demonstrated significantly higher delabeling rates across various label combinations (OR: 10.78, 95% CI: 6.09-19.11, $P < .001$; adjusted OR [aOR]: 10.04, 95% CI: 5.56-18.15, $P < .001$), with the strongest effects seen in PAL+CAL (aOR: 28.36, 95% CI: 10.76-74.80, $P < .001$) and PAL+SAL (aOR: 3.91, 95% CI: 1.17-13.08, $P = .03$). Conversely, differences for the PAL+CAL+SAL and CAL+SAL subgroups were nonsignificant (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). However, given the limited sample sizes, these findings must be interpreted with caution as both subgroups were underpowered to detect true clinical differences. Furthermore, the total number of allergy labels removed per patient favored MAAES in both unadjusted (MD: 0.43, 95% CI: 0.33-0.54, $P < .001$) and adjusted models (adjusted MD: 0.46, 95% CI: 0.35-0.56, $P < .001$). At the initial visit, 829 of 919 (90.2%) labels in MAAES were tested and removed versus 127 (44.6%) in non-MAAES, which required up to 5 visits (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

Time to complete delabeling. MAAES achieved complete delabeling faster than non-MAAES (log-rank $\chi^2 = 42.4$, $P < .001$) (Figure 2), with a median time of 0 months versus 1.4 months (95% CI: 0.90-1.80). Same-day delabeling was substantially more common in the MAAES group (84.9% vs 21.1%; OR: 20.97, 95% CI: 11.82-37.23, $P < .001$), a finding that remained robust after multivariable adjustment (aOR: 19.68, 95% CI: 10.88-35.59, $P < .001$). Because the proportional hazards assumption was violated, we summarize time to delabeling using the cumulative same-day rate and RMST rather than a single hazard ratio. Over 12 months, MAAES shortened

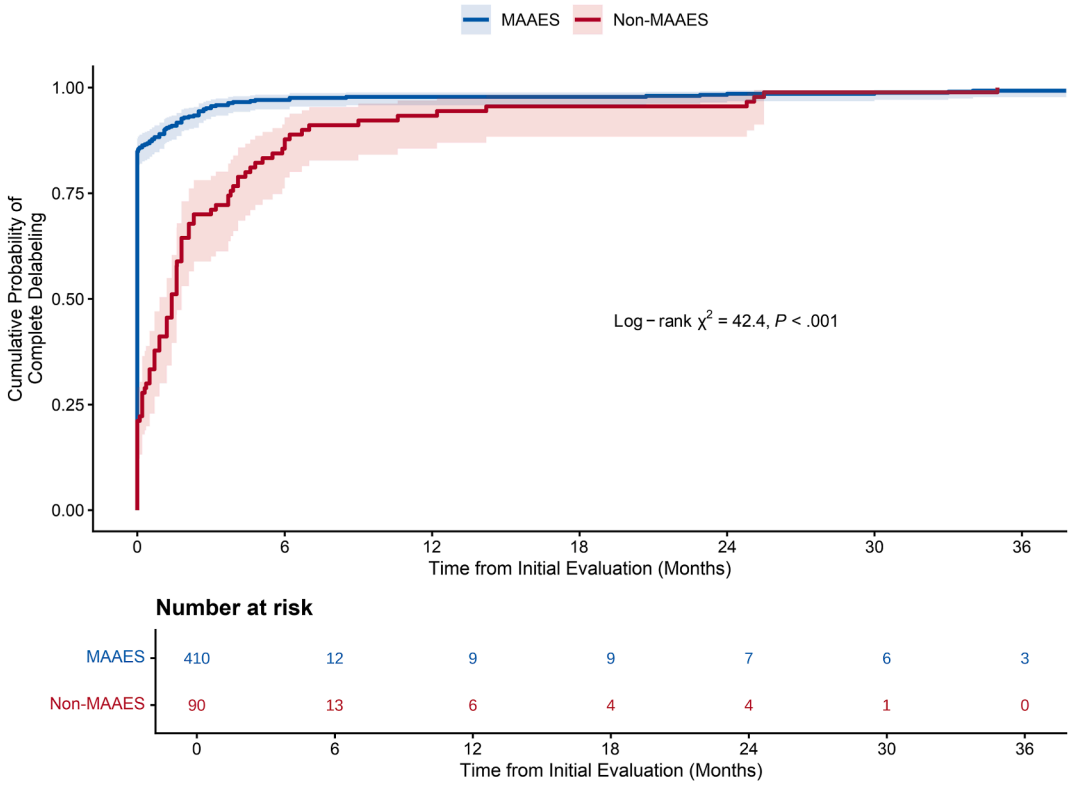

FIGURE 2. Time to fully delabeled antibiotic allergy status in patients undergoing the Multiple Antibiotic Allergy Evaluation Strategy (MAAES) versus non-MAAES evaluation. Kaplan-Meier curves showing the cumulative probability of achieving full antibiotic allergy delabeling over time. Patients undergoing MAAES achieved complete delabeling significantly faster than those undergoing non-MAAES evaluation (log-rank $\chi^2 = 42.4$, $P < .001$).

the time to delabeling by 2.1 months (RMST 0.5 vs 2.6 months). Analysis excluded 78 patients (32 MAAES and 46 non-MAAES) who did not achieve complete delabeling.

Delabeling effectiveness. Loss to follow-up after testing was lower with MAAES, 12 of 919 (1.3%) versus 49 of 285 for non-MAAES (17.2%) (OR: 0.06, 95% CI: 0.03-0.12, $P <$ .001, aOR: 0.06, 95% CI: 0.03-0.13, $P <$ .001). This reduction remained consistent across all drug classes except TMP-SMX (Table E3, available in this article's Online Repository at www.jaci-inpractice.org). Failed challenge leading to lack of delabeling was rare and less frequent with MAAES, 3 of 919 (0.3%) versus 4 of 285 (1.4%) (OR: 0.23, 95% CI: 0.05-1.03, $P = .06$, aOR: 0.30, 95% CI: 0.05-1.94, $P = .21$).

Relabeling rates were significantly lower in the MAAES group (OR: 0.41, 95% CI: 0.23-0.71, $P = .002$; aOR: 0.53, 95% CI: 0.28-0.99, $P = .048$). Cumulative relabeling remained significantly lower for MAAES at every measured time horizon. Within 1 year, relabeling occurred in 2.8% (25 of 895) of the MAAES group versus 7.9% (18 of 227) of the non-MAAES group (OR: 0.33, 95% CI: 0.17-0.66, $P <$ .001). This advantage was sustained through 4 years of follow-up (Table E4, available in this article's Online Repository at www.jaci-inpractice.org).

Safety. AEs were uncommon, occurring in <1% (MAAES) versus 2.8% (non-MAAES) of oral challenges (OR: 0.34, 95% CI: 0.12-0.95, $P = .04$; aOR: 0.26, 95% CI: 0.09-0.78, $P =$ .02). Most reactions were mild, such as urticaria or pruritus, and were managed conservatively, with very low hospitalization rates. Severe AEs were rare, with 1 case per group, both involving TMP-SMX. The MAAES case was a multifocal fixed drug eruption involving skin and genitalia in a patient shown to carry the HLA-B*44:02 associated with TMP-SMX cutaneous reaction,[19] whereas the non-MAAES case was a stroke considered incidental and unrelated to the drug challenge. TMP-SMX was the most frequently implicated antibiotic, with few reactions to cephalexin or amoxicillin (Table III). All MAAES patients (100%) tolerated challenges to nonculprit antibiotics versus 50% in the non-MAAES group. For example, a patient who failed a cephalexin challenge subsequently tolerated cefuroxime and TMP-SMX oral challenges. (Table E5, available in this article's Online Repository at www.jaci-inpractice.org). Importantly, there were no adverse drug events for which drug causality could not be determined.

Survey results

Of 343 patients contacted, 91 responded (26.5%; MAAES: 72, non-MAAES: 19). PRO did not differ significantly between groups across 7 domains in an adjusted cumulative link mixed model (aOR: 0.63, 95% CI: 0.21-1.89, $P = .41$). Results were consistent across individual domains (all $P > .35$) and across alternative analytic approaches, including binary improvement rates, Wilcoxon rank-sum tests, and composite endpoints. A likelihood ratio test showed no evidence of variation in effect

TABLE III. Adverse events during antibiotic challenges in MAAES versus non-MAAES

Outcome	MAAES (n = 919 OC)	Non-MAAES (n = 285 OC)
Any adverse events	9 (0.98)	8 (2.81)
Severe adverse events	1 (0.11)	1 (0.35)
Common adverse events		
Urticaria	4 (0.44)	1 (0.35)
Pruritus without rash	3 (0.33)	3 (1.05)
Lips tingling	1 (0.11)	1 (0.35)
Median onset of reactions (min), IQR	75 (60-120)	60 (52.5-97.5)
Management		
Self-resolved	2 (0.22)	3 (1.05)
Antihistamine	6 (0.65)	4 (1.40)
Hospitalization	1 (0.11)	1 (0.35)
Challenge antibiotic		
Amoxicillin	0	3 (1.05)
Cephalexin	1 (0.11)	1 (0.35)
Trimethoprim-sulfamethoxazole	8 (0.87)	4 (1.40)
Able to pass the other drug challenge	9 (100)	4 (50)

Data are presented as n (%) unless otherwise specified.
IQR, Interquartile range; *MAAES*, Multiple Antibiotic Allergy Evaluation Strategy; *OC*, oral challenge.

across domains ($P = .97$). Adjustment for the number of visits, history of penicillin-associated angioedema, and time from testing to survey completion did not materially change estimates (Figure 3). A composite PRO score (mean across all domains on a −2 to +2 scale) was similar between groups (MAAES: 0.37 ± 0.68 vs non-MAAES: 0.50 ± 0.54; difference −0.14, $P = .36$), with both groups reporting net improvement. Worsening in at least 1 domain was similar between MAAES (35%) and non-MAAES (42%) patients ($P = .60$), with no individual domain reaching statistical significance after multiplicity adjustment.

Post-2020 restricted analysis

In the post-2020 subcohort (n = 308; MAAES 257, non-MAAES 51), the MAAES strategy maintained a significant advantage for combination delabeling (aOR: 8.83, 95% CI: 3.71-21.00, $P < .001$) (Table E6, available in this article's Online Repository at www.jaci-inpractice.org), confirming its efficacy during the era of widespread direct oral challenges. Other outcomes were consistent with the primary analysis, including a 2.1-month reduction in 12-month RMST (0.3 vs 2.4 months) and same-day delabeling (Table E6, available in this article's Online Repository at www.jaci-inpractice.org). Delabeling effectiveness remained stable, with no significant differences in loss to follow-up, failed oral challenges, or relabeling between the primary and post-2020 cohorts (Table E6, available in this article's Online Repository at www.jaci-inpractice.org).

Propensity-score sensitivity analysis

Propensity scores showed substantial overlap between groups, and IPTW reduced absolute standardized MDs across all covariates to below the 0.10 threshold (Figure E2, available in this article's Online Repository at www.jaci-inpractice.org). After IPTW adjustment, the OR for combination delabeling remained robust (OR: 8.93, 95% CI: 4.78-16.70, $P < .001$), consistent with unadjusted and multivariable-adjusted estimates (Table E7, available in this article's Online Repository at www.jaci-inpractice.org). The IPTW 12-month RMST difference was highly concordant with primary analyses (Table E7, available in this article's Online Repository at www.jaci-inpractice.org). Matching-style robustness analysis produced point estimates in the same direction. Together, the multivariable and propensity-score sensitivity analyses indicate that the primary association between MAAES and delabeling cannot be attributed to baseline imbalance in measured covariates.

DISCUSSION

Multiple AAL involving first-line antibiotics such as penicillins, cephalosporins, and TMP-SMX are common and frequently inaccurate,[1-3] yet they restrict access to first-line therapies and are associated with worse clinical outcomes.[7-10] Traditional evaluation strategies typically address one label per visit, which can prolong time to delabeling and increase the risk of incomplete evaluation. In this study, a consolidated approach using MAAES significantly improved delabeling outcomes with a low observed AE rate and favorable PRO.

MAAES demonstrated superior delabeling efficacy, removing 97.4% of labels compared with 79.6% for non-MAAES (aOR: 9.41, 95% CI: 5.22-16.95, $P < .001$). The MAAES advantage remained robust in the post-2020 subcohort analysis (aOR: 8.83, 95% CI: 3.71-21.00, $P < .001$), confirming that the efficiency gains are attributable to the consolidated workflow rather than temporal shifts toward direct oral challenges. Furthermore, IPTW propensity-score sensitivity analysis confirmed that these results are not attributed to baseline imbalances in patient history or complexity.

MAAES substantially shortened the time to complete delabeling, with 84.9% of patients fully delabeled on the same day versus 21.1% in the non-MAAES pathway (median time 0 vs 1.4 months). By accelerating the removal of inaccurate labels, this approach may enable earlier access to first-line antibiotics during future infections, supporting antimicrobial stewardship. Previous studies indicate that delabeling increases appropriate narrow-spectrum use and reduces broad-spectrum therapy within weeks of testing.[20,21]

MAAES also showed improved effectiveness in real-world care delivery by significantly reducing loss to follow-up (1.3% vs 17.2%; aOR: 0.06, 95% CI: 0.03-0.13, $P < .001$). This finding reflects a structural advantage of the MAAES protocol, which minimizes the logistical burden on patients by eliminating the need for multiple return visits, ensuring higher evaluation completion rates than traditional sequential testing.

Regarding durability, the lower risk of relabeling persisted after adjustment, though attenuated and of borderline significance (aOR: 0.53; 95% CI: 0.28-0.99, $P = .048$), an advantage sustained through 4 years of follow-up. Although our 1-year relabeling rate (2.8%) is lower than previously reported (approximately 25%),[16] these findings should be considered hypothesis-generating. We hypothesize that consolidated evaluation reduces fragmented messaging across encounters, while reinforcing results through after-visit summaries[16] and direct primary care communication mitigates administrative re-entry errors.

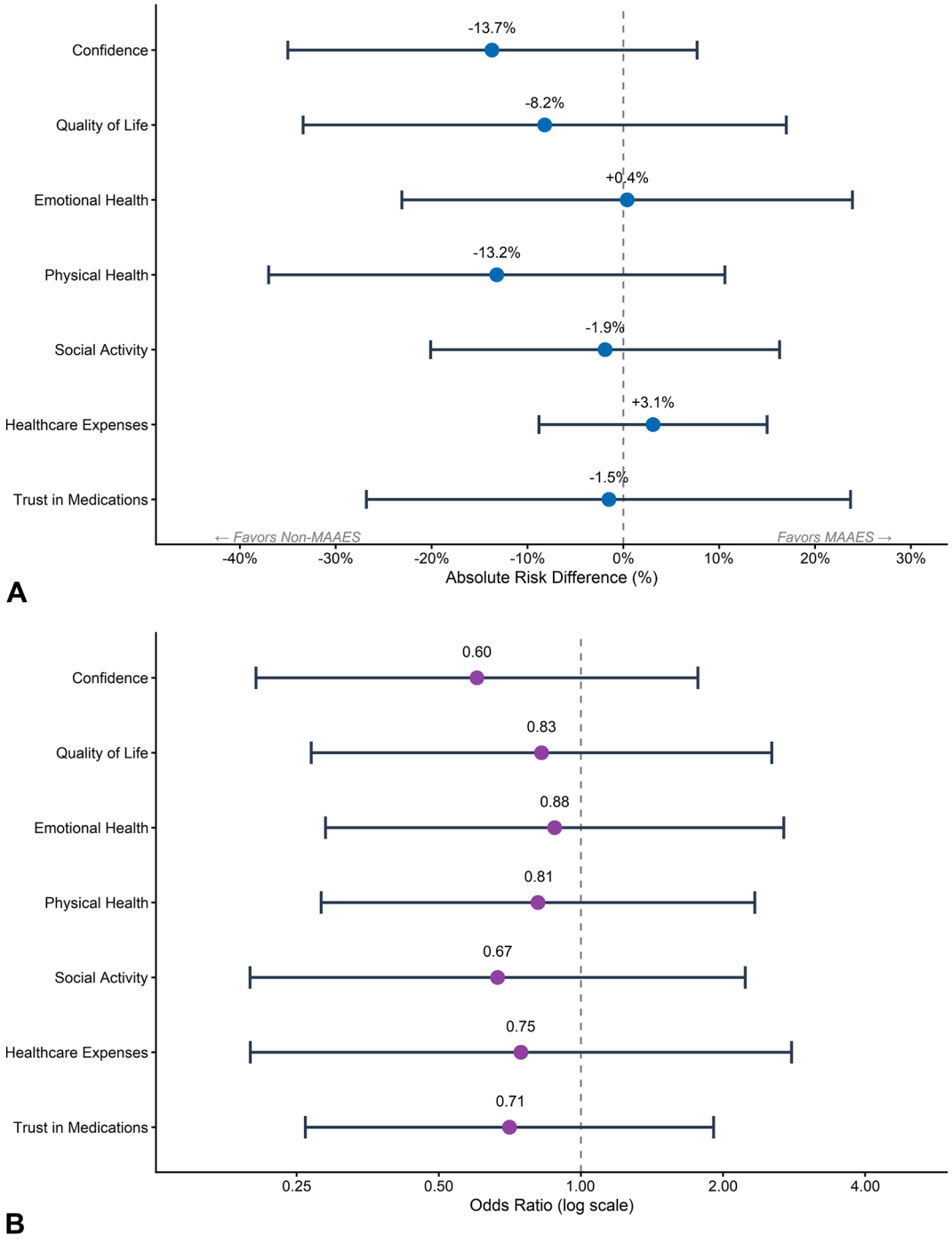

FIGURE 3. Patient-reported outcome improvements after antibiotic allergy evaluation: Multiple Antibiotic Allergy Evaluation Strategy (MAAES) versus non-MAAES. (**A**) Forest plot showing absolute differences in improvement rates between the MAAES and non-MAAES pathways across patient-reported outcome domains. Positive values favor MAAES. Points represent absolute risk differences, and horizontal bars indicate 95% confidence intervals. (**B**) Adjusted ordinal regression evaluating the association between MAAES and improvement across the same domains. Odds ratios were adjusted for total visits, history of angioedema, and time to survey completion. Points represent adjusted odds ratios, and horizontal bars indicate 95% confidence intervals; the vertical dashed line at 1 indicates no difference.

MAAES demonstrated a favorable safety profile with a lower AE rate than non-MAAES (<1% vs 2.8%; aOR: 0.26, 95% CI: 0.09-0.78, $P = .02$). Most reactions were mild and self-limited. Severe events were rare in both groups. The use of MAAES did not result in increased intolerance or difficulty identifying the specific culprit drug during AEs. Causality was resolved in every

instance. This success likely stems from selecting patients with low-risk histories and low pretest probability of true allergy, which directly contributed to the favorable safety profile. These findings reinforce that, at present, MAAES should be reserved for patients meeting these low-risk criteria.

Evaluation pathway selection appeared to be influenced by clinical history and patient preference. The non-MAAES group had a higher prevalence of prior higher-risk penicillin histories, including anaphylaxis and angioedema. However, these reactions were remote and outside the predefined high-risk exclusion window. In addition, some patients opted for a traditional multivisit approach. These findings suggest that provider-perceived risk and patient preference significantly influence the implementation of consolidated testing strategies.

Finally, although the 26.5% survey response rate and small non-MAAES subgroup (n = 19) limit a definitive conclusion of equivalence, PRO were broadly similar between groups. After adjusting for the 68-month average interval since testing, both cohorts reported net improvements in confidence and quality of life. These exploratory data suggest that the MAAES approach improves clinical efficiency without compromising the long-term patient experience.

The absence of a perceived difference may reflect that patients undergoing MAAES do not recognize the single-visit approach as distinct from standard care, particularly in centers where consolidated challenges become routine. Furthermore, the 68-month average follow-up likely attenuated recall of the clinic experience, whereas downstream benefits of delabeling persist regardless of strategy. These findings highlight the need for prospective assessments conducted closer to the time of testing, particularly in centers where MAAES is newly implemented.

Several limitations warrant consideration. First, the retrospective design limits causal inference. Treatment pathways were determined by clinician judgment and patient preference, introducing potential residual confounding. For instance, the 23.5% of the cohort who underwent non-MAAES evaluation likely represent a subset with higher baseline anxiety, logistical constraints, or specific provider-perceived risks. Although multivariable adjustment and IPTW mitigated baseline differences, unmeasured factors such as patient motivation or provider communication may still contribute to residual confounding. Second, this single-center study in an outpatient setting may lack generalizability to inpatient populations. Our cohort was predominantly White, female, and included 15% out-of-state travelers, representing a highly motivated population. Although these limit broad generalizability, these demographics underscore the clinical necessity of MAAES, as travel burdens were primary drivers for developing a single-visit solution. Third, although practice patterns evolved toward direct oral challenges over 10 years, a restricted analysis of the post-2020 cohort confirmed that the MAAES advantage remains robust. Fourth, the 26.5% survey response rate and small non-MAAES subgroup limit the power to detect differences in PRO. The survey's 68-month average follow-up likely introduced significant recall bias and lowered the response rate, as nonresponders may have found the evaluation no longer relevant. In addition, the reliance on email and patient portals may have introduced digital-engagement bias. Finally, our relabeling definition included all EHR re-entries, as we could not consistently distinguish clinical reactions from clerical errors. Regardless of the mechanism, these represent a failure in durability that restricts antibiotic access. To mitigate this at our facility, all patients received formal discharge summaries and instructions to provide documentation to their primary care providers.

Future studies should evaluate the cost-effectiveness of consolidated testing models, their impact on antibiotic prescribing patterns and antimicrobial resistance, and implementation across diverse clinical settings, including inpatient and perioperative populations. Given our findings on safety, effectiveness, and durability, we recommend policy changes to reimburse multiple same-day drug challenges in jurisdictions currently requiring sequential office visits for single labels.

CONCLUSIONS

For patients with multiple low-risk antibiotic allergies, the MAAES strategy improved delabeling efficacy and effectiveness compared with traditional care, without compromising safety. These results support single-visit, multilabel evaluation as a practical, high-value approach. Future research should evaluate implementation across diverse clinical settings to optimize delivery.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work the author(s) used ChatGPT (OpenAI) and Gemini Pro (Google) in order to assist with language editing, improving readability, and generating a visual summary. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

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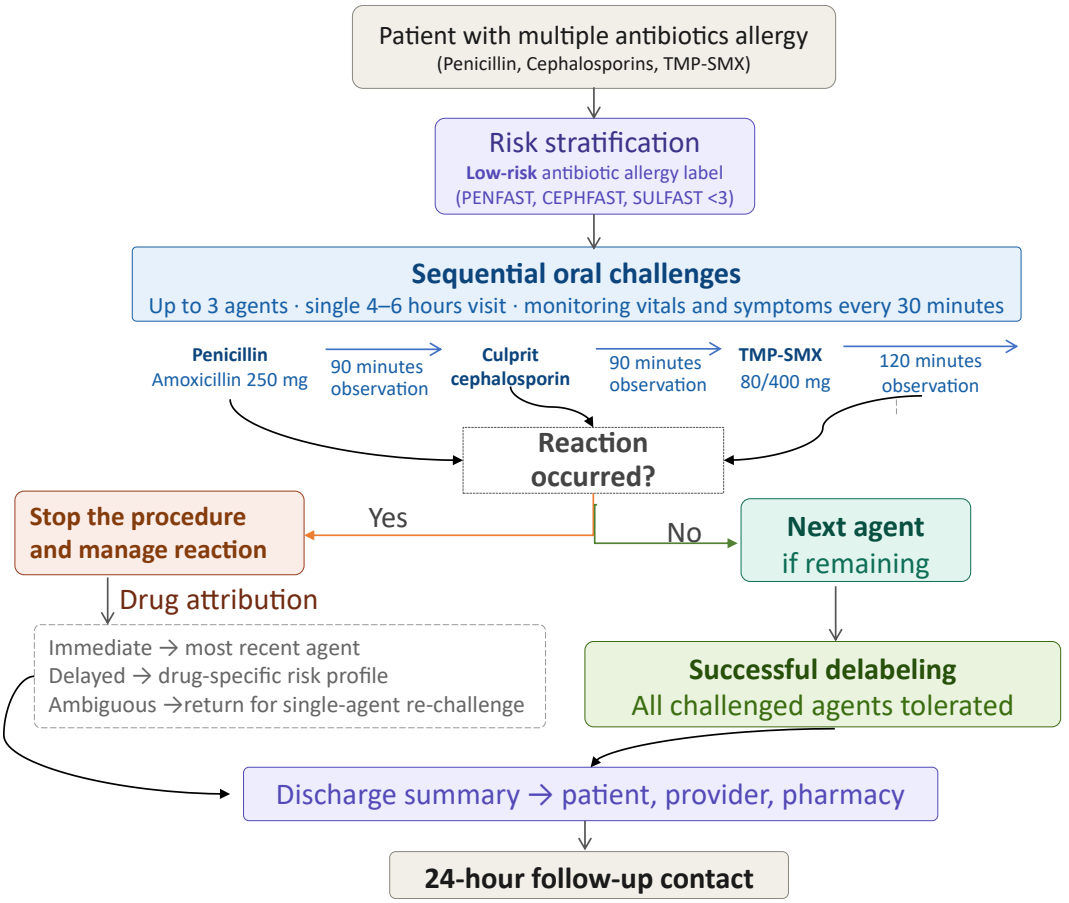

FIGURE E1. The MAAES protocol. A single-visit, sequential delabeling strategy for low-risk patients. Evaluation includes indicated skin testing and up to 3 oral challenges. Immediate reactions are attributed to the most recent agent (90- to 120-minute window), whereas delayed reactions prioritize sulfonamide attribution. Successful delabeling is finalized via clinical loop-closure with patients, providers, and pharmacies. Note: Patients with multiple cephalosporin labels were managed based on clinical history and R1-group side-chain cross-reactivity. Low-risk patients generally underwent a direct oral challenge to the culprit agent. For multilabel cases, an "optimal drug" strategy was used: patients were challenged with a clinically relevant cephalosporin with a dissimilar R1 side chain to confirm a safe, functional alternative. *MAAES*, Multiple Antibiotic Allergy Evaluation Strategy; *TMP-SMX*, trimethoprim-sulfamethoxazole.

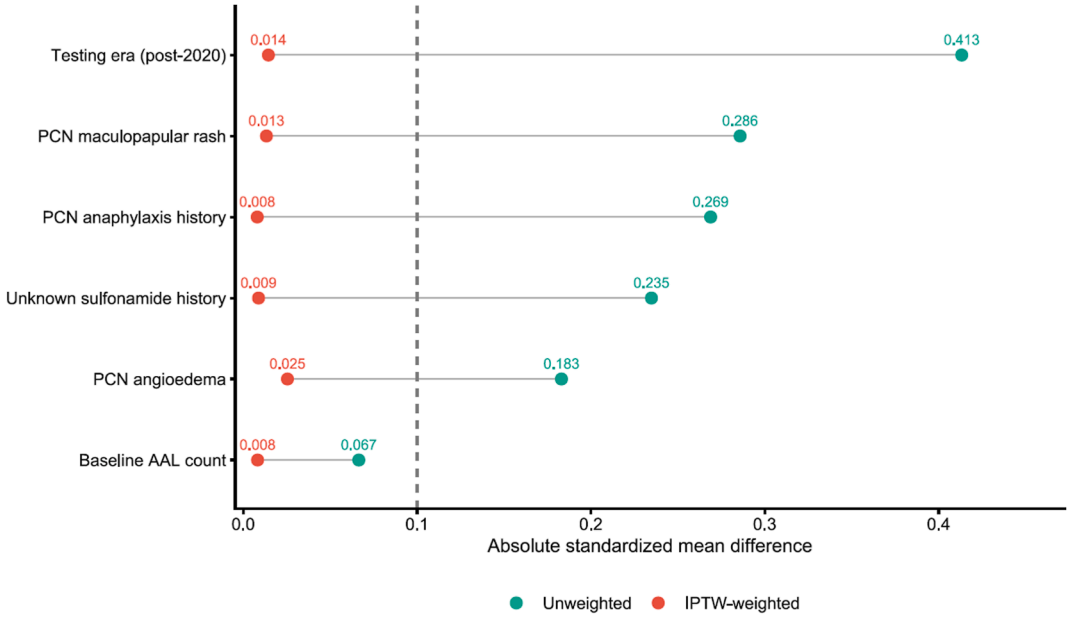

FIGURE E2. Covariate balance before and after inverse probability of treatment weighting (IPTW). Absolute standardized mean differences (ASMD) for prespecified covariates and baseline AAL count are shown before (green, unweighted) and after stabilized IPTW (red, weighted) based on propensity scores. The dashed line indicates the balance threshold (ASMD <0.10). IPTW reduced all covariates below 0.10, indicating adequate covariate balance after weighting. *AAL*, Antibiotic allergy label; *PCN*, penicillin.

TABLE E1. Antibiotic allergy testing modalities, visit distribution, and delabeling outcomes by evaluation pathway

	Penicillin		Cephalosporins		Trimethoprim-sulfamethoxazole		Total	
Drug allergy tested	**MAAES (388 labels)**	**Non-MAAES (127 labels)**	**MAAES (273 labels)**	**Non-MAAES (93 labels)**	**MAAES (258 labels)**	**Non-MAAES (65 labels)**	**MAAES (919 labels)**	**Non-MAAES (285 labels)**
Type of testing								
SPT	–	17 (13.4)	–	49 (52.7)	–	1 (1.5)	–	67 (23.5)
SPT+OC	291 (75.0)	102 (80.3)	208 (76.2)	41 (44.1)	2 (0.8)	0 (0)	501 (54.5)	143 (50.2)
DOC	97 (25.0)	8 (6.3)	65 (23.8)	3 (3.2)	256 (99.2)	64 (98.5)	418 (45.5)	75 (26.3)
Labels tested								
1st visit	371 (95.6)	118 (92.9)	254 (93.0)	79 (85.0)	237 (91.9)	15 (23.1)	862 (93.8)	212 (74.4)
2nd visit	17 (4.4)	8 (6.3)	18 (6.6)	11 (11.8)	20 (7.8)	40 (61.5)	55 (6.0)	59 (20.7)
3rd visit	0 (0)	1 (0.8)	1 (0.4)	3 (3.2)	1 (0.3)	5 (7.7)	2 (0.2)	9 (3.1)
4th visit	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (6.2)	0 (0)	4 (1.4)
5th visit	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.5)	0 (0)	1 (0.4)
Labels removed								
1st visit	361 (93)	94 (74.0)	245 (89.7)	20 (21.5)	223 (86.4)	13 (20.0)	829 (90.2)	127 (44.6)
2nd visit	21 (5.4)	16 (12.6)	21 (7.7)	27 (29.0)	22 (8.5)	36 (55.4)	64 (7.0)	79 (27.7)
3rd visit	0 (0)	2 (1.6)	1 (0.4)	9 (9.7)	1 (0.4)	5 (7.7)	2 (0.2)	16 (5.6)
4th visit	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (6.2)	0 (0)	4 (1.4)
5th visit	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.5)	0 (0)	1 (0.4)
Total delabel	382 (98.5)	112 (88.2)	267 (97.8)	56 (60)	246 (95.3)	59 (90.8)	895 (97.4)	227 (79.6)

Data are presented as n (%).
DOC, Direct oral challenge; *MAAES*, Multiple Antibiotic Allergy Evaluation Strategy; *OC*, oral challenge; *SPT*, skin prick testing.

TABLE E2. Delabeling success by antibiotic combination

Drug combination	MAAES	Non-MAAES	OR (95% CI), *P* value	Adjusted OR* (95% CI), *P* value
PAL+CAL	178/185 (96.2)	37/71 (52.1)	23.37 (9.62-56.74), <.001	28.36 (10.76-74.80), <.001
PAL+SAL	162/169 (95.9)	36/43 (83.7)	4.50 (1.49-13.63), .01	3.91 (1.17-13.08), .03
CAL+SAL	49/54 (90.7)	6/9 (66.7)	4.90 (0.93-25.86), .06	3.51 (0.63-19.59), .15
PAL+CAL+SAL	33/34 (97.1)	11/13 (84.6)	6.00 (0.49-72.77), .16	2.70 (0.13-54.83), .52

Data are presented as n/N (%) unless otherwise specified.
CAL, Cephalosporins allergy labels; *CI*, confidence interval; *MAAES*, Multiple Antibiotic Allergy Evaluation Strategy; *OR*, odds ratio; *PAL*, penicillin allergy labels; *SAL*, sulfonamide allergy labels.
*Adjusted for history of penicillin anaphylaxis, angioedema, maculopapular rash, unknown sulfonamide history, and testing era (post-2020 vs earlier).

TABLE E3. Loss to follow-up after antibiotic allergy evaluation stratified by drug class

Drug	MAAES	Non-MAAES	OR (95% CI), *P* value	Adjusted OR* (95% CI), *P* value
Penicillin	6/388 (1.5)	11/127 (8.7)	0.17 (0.06-0.46), <.001	0.15 (0.06-0.42), <.001
Cephalosporins	1/273 (0.4)	36/93 (38.7)	0.01 (0.00-0.04), <.001	0.01 (0.00-0.04), <.001
Trimethoprim-sulfamethoxazole	5/258 (1.9)	2/65 (3.1)	0.62 (0.12-3.29), .60	0.62 (0.11-3.44), .583
Total	12/919 (1.3)	49/285 (17.2)	0.06 (0.03-0.12), <.001	0.06 (0.03-0.13), <.001

Data are presented as n/N (%) unless otherwise specified. Loss to follow-up was defined as patients who did not complete the planned evaluation pathway after initial testing.
CI, Confidence interval; *MAAES*, Multiple Antibiotic Allergy Evaluation Strategy; *OR*, odds ratio.
*Adjusted for history of penicillin anaphylaxis, angioedema, maculopapular rash, unknown sulfonamide history, and testing era (post-2020 vs earlier).

TABLE E4. Cumulative relabeling rates by time since delabeling

Time horizon	MAAES (n = 895)	Non-MAAES (n = 227)	Odds ratio (95% CI)	*P* value
1 year	25 (2.8)	18 (7.9)	0.33 (0.17-0.66)	<.001
2-year	38 (4.2)	24 (10.6)	0.38 (0.21-0.67)	<.001
3-year	43 (4.8)	30 (13.2)	0.33 (0.20-0.56)	<.001
4-year	44 (4.9)	31 (13.7)	0.33 (0.20-0.55)	<.001

Data are presented as n (%) unless otherwise specified. Relabeling refers to the reappearance of an antibiotic allergy label after prior delabeling. Odds ratios and *P* values in this table represent unadjusted cumulative rates at each annual time horizon. In the final multivariable-adjusted model accounting for baseline covariates, the overall lower risk of relabeling in the MAAES group attenuated from an unadjusted odds ratio of 0.41 to an adjusted odds ratio of 0.53 ($P = .048$). This adjusted finding demonstrated borderline significance and did not survive multiple-comparison correction (Holm $P = .095$; Benjamini-Hochberg $P = .064$), whereas primary outcomes for delabeling, loss to follow-up, and adverse events remained statistically significant.
CI, Confidence interval; *MAAES*, Multiple Antibiotic Allergy Evaluation Strategy.

TABLE E5. Clinical characteristics of reactions observed during antibiotic oral challenges: MAAES = A1-A9, non-MAAES = B1-B8

Case	Drug	Reaction type	Onset	Treatment	Skin testing prior OC (SPT/IDT)	Same-day OC with other drugs	Other antibiotic labels/continued OCs	Notes
A1	Cephalexin	Mild pruritus	30 min	ATH	SPT positive	No	Passed cefuroxime and TMP-SMX OC later	
A2	TMP-SMX	Urticaria (3 lesions)	60 min	ATH	None	Yes	Passed amoxicillin OC	
A3	TMP-SMX	Urticaria (single hive)	75 min	ATH	None	Yes	Passed cephalexin OC	Hive over lymph node near prior infection site
A4	TMP-SMX	Urticaria (face/trunk)	14 min after 2nd dose	ATH	SPT positive	No	Passed PCN and ceph OC prior	
A5	TMP-SMX	Urticaria	2.5 h	ATH	SPT positive	No	Passed PCN and ceph prior	Heat/dermographism confound
A6	TMP-SMX	Lip tingling + nausea	2 h	None	SPT positive	Yes	Passed cefdinir OC	Underlying—not well-controlled migraine
A7	TMP-SMX	Pruritus + throat irritation	1.5 h	ATH	SPT positive	No	Passed PCN and ceph OC prior	
A8	TMP-SMX	Pruritus + throat irritation	30 min	None	None	No	Passed PCN and ceph OC prior	Self-resolved
A9	TMP-SMX	Multifocal fixed drug eruption	4 h	Hospitalized	None	Yes	Passed PCN OC same visit; cephalexin later	HLA-B*44:02 associated with TMP-SMX SCARs
B1	Amoxicillin	GI upset + pruritus	20 min	ATH	IDT negative PCN	Pen VK given before amoxicillin challenge (history of ampicillin-sulbactam allergy)	Cefpodoxime label persists (did not return for OC)	Recommendation - consider amoxicillin with ATH
B2	Amoxicillin	Headache + fatigue	1.5 h	None	SPT/IDT negative PCN	None	Cephalexin and cefaclor labels persist	Blood pressure 173/68 mm Hg at the visit
B3	Amoxicillin	Pruritus	60 min	ATH+TCS	IDT negative PCN	None	Avoid amoxicillin/clavulanic acid	Safe for other penicillins
B4	Cephalexin	Pruritus without rash	60 min	ATH	IDT negative ceph	Same patient as B3	Cefdinir label persists	Dermatographism; use ATH
B5	TMP-SMX	Malaise + feeling hot	4 h	Hospitalized	None	None	Passed amoxicillin and cephalexin OC	Initially left clinic but returned with malaise and feeling hot. Observed 2 hours after returning. Then later hospitalized for encephalopathy
B6	TMP-SMX	Erythema and warmth	7-8 h	ATH	None	None	Passed cephalexin OC	Likely sulfamethoxazole component
B7	TMP-SMX	Urticaria (3 hives)	30 min	None	None	None	Passed amoxicillin OC	
B8	TMP-SMX	Lip/tongue tingling	30-60 min	Self-resolved	None	None	Passed amoxicillin OC	Consider future placebo challenge

Common adverse events listed here represent a partial list of observed reactions.

ATH, Antihistamine; *ceph*, cephalosporin; *IDT*, intradermal testing; *MAAES*, Multiple Antibiotic Allergy Evaluation Strategy; *OC*, oral challenge; *PCN*, penicillin; *SCAR*, severe cutaneous adverse reaction; *SPT*, skin prick testing; *TCS*, topical corticosteroid; *TMP-SMX*, trimethoprim-sulfamethoxazole.

TABLE E6. Post-2020 subcohort sensitivity analysis

Outcome	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)*	*P* value
Combination antibiotic delabeled (patient-level)	9.32 (3.97-21.87)	<.001	8.83 (3.71-21.00)	<.001
Same-day delabeling	36.94 (14.62-93.34)	<.001	42.53 (15.72-115.03)	<.001
Loss to follow-up	0.08 (0.03-0.20)	<.001	0.08 (0.03-0.20)	<.001
Failed challenge	0.10 (0.01-1.08)	.06	0.10 (0.01-1.17)	.07
Relabeled	0.99 (0.12-7.95)	.10	1.01 (0.13-8.08)	.10

CI, Confidence interval; *OR*, odds ratio.
*Adjusted for history of penicillin anaphylaxis, angioedema, maculopapular rash, and unknown sulfonamide history.

TABLE E7. Sensitivity analysis of delabeling efficacy and time to complete delabeling using multiple adjustment strategies

Model strategy	Combination antibiotic delabeled (patient-level) OR (95% CI)	RMST difference (mo)
Unadjusted	10.78 (6.09-19.11)	2.1
Multivariable adjusted	10.04 (5.56-18.15)	2.1
Stabilized IPTW	**8.93 (4.78-16.70)**	**1.9**
Caliper matched	3.26 (1.90-5.58)	—

Bold text shows the IPTW results.
$P < .001$ for all estimates.
CI, Confidence interval; *IPTW*, inverse probability of treatment weighting; *OR*, odds ratio; *RMST*, restricted mean survival time.