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MAJOR ARTICLE

Direct Oral Challenge for Penicillin Allergy: The International Network of Antibiotic Allergy Nations (iNAAN) Study

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Background. Approximately 10% of hospitalized patients globally report a penicillin allergy, leading to inappropriate antibiotic prescribing and inferior healthcare outcomes. Evidence supporting the effectiveness and widespread implementation of inpatient penicillin direct oral challenge (DOC) is limited.

Methods. A prospective, multicenter, international type 2 hybrid effectiveness-implementation study was conducted in 40 hospitals across 8 countries between November 2022 and May 2025. Adult inpatients with a penicillin allergy underwent assessment using a digital penicillin allergy toolkit (National Antibiotic Allergy Network [NAAN] App). According to site clinical practice, participants received penicillin DOC (effectiveness intervention) or assessment only. Participating sites received bimonthly audit and feedback at least 3 months after site activation (implementation strategy). Observational data were used to emulate a target trial to examine secondary effectiveness outcomes, including antibiotic prescribing at 90 days in DOC versus non-DOC participants. The primary implementation outcome was adoption of the NAAN App within 6 months of site activation.

Results. Among 5121 participants assessed, 1573 (30.7%) underwent DOC, of which 1502 (95.5%) were delabeled. Of 71 (4.5%) participants with a positive DOC, 6 (0.4%) had a serious adverse event. Of 1852 inpatients in the target trial analysis, 892 underwent DOC and 960 underwent assessment only. Participants who underwent DOC were more likely to be prescribed penicillin (risk ratio [RR], 13.25 [95% confidence interval {CI}, 7.82–22.46]), and less likely to be prescribed World Health Organization (WHO) "Watch" or "Reserve" antibiotics (RR, 0.73 [95% CI, .60–.89]) at 90 days post evaluation. Within 6 months of site activation, 77 clinicians adopted the NAAN App.

Conclusions. Multidisciplinary adoption of inpatient penicillin DOC was safe and significantly improved penicillin prescribing and reduced use of WHO restricted antibiotics.

Keywords. allergy; antibiotic allergy; direct oral challenge; delabeling; antimicrobial stewardship.

Approximately 10% of people globally are labeled as penicillin allergic [1], with well-described negative impacts on clinical care and outcomes from published regional experiences [2]. The downstream effects of self-reported penicillin allergy include an increased risk of suboptimal antibiotic prescribing, multidrug-resistant infections, extended hospital length of stay (LOS), and hospital readmission [3–6].

Recent efforts to address the burden of penicillin allergy include the development of internationally validated assessment tools to define "low-risk" penicillin allergy and identify patients appropriate for direct oral challenge (DOC) [7]. Among low-risk patients, randomized controlled trial (RCT) data support DOC as noninferior to skin testing followed by oral challenge [8, 9], but such studies have primarily been conducted in ambulatory populations.

Beyond local regional experiences [10–13], the broader use of non-allergist-delivered penicillin DOC to enable delabeling, including in areas where allergists are not available, remains ill-defined. Data in understudied regions (eg, rural and remote healthcare) and populations (eg, immunocompromised hosts [ICHs]) is also needed. Additionally, the impact of inpatient penicillin DOC on antibiotic prescribing across different jurisdictions, including the effect on prescribing World Health Organization (WHO) "Watch" and "Reserve" antibiotic classes, is unknown. Finally, while implementation strategies have been used for other antimicrobial stewardship (AMS) interventions [14], they have not previously been examined in allergy-AMS practice to understand if DOC can be scaled globally.

The International Network of Antibiotic Allergy Nations (iNAAN) was a multinational study that aimed to prospectively evaluate the safety and effectiveness of multidisciplinary-led inpatient penicillin DOC in hospitals with an existing or newly established penicillin allergy delabeling program. Implementation of the DOC intervention was also assessed.

METHODS

Study Design Overview

iNAAN was an international, multicenter, prospective type 2 hybrid effectiveness-implementation study. As previously described [15], the iNAAN study was conducted in 40 hospitals in 8 countries including Australia, South Africa, Malaysia, the United Kingdom, Hong Kong, Canada, the United States, and New Zealand (Supplementary Table 1). The study protocol (Supplement 2) was initially approved by the Austin Health Human Research Ethics Committee (HREC78719/Austin-2021) and then by individual independent institutional review boards at each participating hospital. The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12623000484640) on 12 May 2023.

A National Antibiotic Allergy Network smartphone application (NAAN App) was developed and deployed to aid multidisciplinary clinicians in performing a point-of-care penicillin allergy risk assessment and to enable standardized data collection in all participants. The NAAN App produced a phenotypic risk assessment using an adapted version of a validated antibiotic allergy assessment tool (AAAT) [16] and PEN-FAST clinical decision rule to aid clinician assessment (Supplementary Figures 1 and 2) [17]. Individual NAAN App access and training were provided to investigators and their delegates at the time of site activation. The principal aim of the NAAN App was to enable quantification of users as a definition of clinician adoption of penicillin allergy evaluation.

Following allergy assessment, eligible inpatients received penicillin DOC ("intervention"). Simultaneously, audit and

feedback was deployed as an "implementation strategy." The safety of inpatient penicillin DOC and clinician adoption of the NAAN App were co-primary outcomes.

A waiver of consent was approved for the collection of data when penicillin allergy assessment and DOC were performed as part of routine clinical practice. Written informed consent was sought from participants if a waiver of consent was not approved by the local institutional review board. Data were managed and stored using REDCap electronic data capture tools [18, 19], hosted by BioGrid Australia. Study oversight and statistical analysis were performed at Austin Health, Victoria, Australia.

Participants

Participants were hospitalized patients aged ≥18 years who reported a penicillin allergy and underwent a clinician-led point-of-care penicillin allergy assessment using the NAAN App. Participants were defined as low risk in accordance with local site protocols. They were excluded if a penicillin allergy assessment could not be performed or a reliable history could not be ascertained. Participants were identified by multidisciplinary clinicians, including doctors, nurse practitioners, nurses, and pharmacists at participating hospitals.

Effectiveness Interventions

Participants identified as having a low-risk penicillin allergy as per previous definition were offered a DOC conducted according to the site clinical protocol. Those who reported a type A history, a nonimmunologic or direct "on-target" adverse drug reaction, or who had demonstrated tolerance of penicillin since the index reaction were offered "direct delabel" of their allergy or a DOC, depending on participant and clinician preference. Positive DOC events were adjudicated by the local clinician, including serious adverse events (SAEs), defined as events leading to death, a life-threatening reaction, intensive care unit admission or hospital readmission, persistent or significant disability/incapacity, or an event that requires intervention to prevent permanent impairment or damage [20]. Positive DOC events were independently reviewed by 2 physicians, both with drug allergy expertise and independent of the study, with review by an additional physician when consensus was not achieved (Supplementary Methods).

Implementation Strategy

The implementation strategy was initiated at each site at least 3 months post–site activation. Clinicians received audit and feedback, delivered bimonthly, known as the iNAAN Health Service Report. Sites were audited against their local clinical penicillin allergy guideline. The site-specific iNAAN Health Service Report encompassed aggregate data with the sites' local clinical effectiveness and implementation outcomes of inpatient penicillin DOC, including the number and safety of penicillin DOC and activity by discipline, with site-level benchmarking (Supplementary Figure 3) [21].

Data Collection

Using the NAAN App with direct linkage to the REDCap database, data were collected from participants and health service medical records at the time of assessment and DOC. Participants' ethnicity and race were classified following the subcategories for the country of recruitment and obtained from the medical record or verbal confirmation with the participant. At 90 days post–penicillin allergy evaluation, the participants' subsequent antibiotic prescribing, infection, and other health-related outcomes were evaluated by site personnel using the local hospital medical record.

Outcomes

Effectiveness

The primary effectiveness outcome was safety, defined as the proportion of participants with a low-risk penicillin allergy who were delabeled following DOC. This was calculated as the number of participants delabeled via DOC divided by the number of participants who underwent DOC. Delabeled was defined as removal of the penicillin allergy label following exclusion of an immediate or delayed positive DOC, as determined by the site clinician.

The secondary effectiveness outcomes are described in Supplementary Table 2 and include prescribing of penicillin and restricted antibiotics post evaluation, presence of multidrug-resistant organisms and *Clostridioides difficile* infection, and hospital LOS post evaluation. The effect of penicillin DOC on antibiotic prescribing among low-risk hospitalized patients was assessed using a target trial emulation (TTE) approach [22], with the statistical analysis plan and TTE framework finalized prior to data censure. Additionally, the effect of any delabeling, either via DOC or direct delabeling (ie, removal of a patient's reported penicillin allergy via medical reconciliation alone), on named secondary effectiveness outcomes (penicillin use, restricted antibiotic use, and hospital LOS) was also examined.

Implementation

The primary implementation outcome was clinician adoption of the NAAN App, defined as the change in the number of active NAAN App users from baseline to 6 months post–site activation. Secondary implementation outcomes, including the effect of the implementation strategy and sustainability, will be presented in a subsequent manuscript.

Study data were collected from 9 November 2022 to 7 May 2025.

Statistical Analysis

According to a previous inpatient penicillin allergy delabeling study conducted in 2 Australian hospitals [23], we estimated the number of participants who would undertake inpatient penicillin DOC in up to 40 iNAAN hospitals to be 400 per

year; however, site activation and participant recruitment were not capped. The defined timepoint for analysis of primary and secondary outcomes was when a minimum of 1000 inpatient penicillin DOCs had been performed and when more than 85% of activated hospitals had received at least 3 episodes of audit and feedback.

Statistical analysis was performed using Stata 18 software (StataCorp, College Station, TX, USA). Descriptive statistics were presented as median (interquartile range [IQR]) or frequency (percentage). The primary effectiveness outcome was expressed as count and percentage with 95% confidence intervals (CIs). Additional analyses included subgroup analysis by multidisciplinary clinician group, country, hospital peer group, and PEN-FAST score.

A TTE framework was used to evaluate secondary effectiveness outcomes of antibiotic prescribing and antimicrobial resistance (AMR) for inpatients with a predefined low-risk penicillin allergy using the iNAAN dataset [22]. The inclusion criteria were adult inpatients with an immune-mediated or unknown low-risk penicillin allergy label, defined as PEN-FAST score <3 [17] or "green" on the AAAT [16], ascertained by the NAAN App. Only predefined low-risk participants were identified for inclusion in the TTE analysis as when mimicking an RCT, ethical and clinical safety concerns would not permit high-risk participants to be randomized to intervention. Detailed inclusion and exclusion criteria are in Supplementary Table 3. The statistical analysis mimicked per-protocol analysis of the target trial using inverse probability of treatment weighting approach. Weights were derived using an entropy balancing approach. Antibiotic utilization was defined as the number of participants receiving at least 1 dose of the antibiotic of interest. A generalized linear model with binomial family, log link, and robust variance estimator was used to assess antibiotic prescribing and AMR between those delabeled via DOC versus those not delabeled. Hospital LOS was compared using linear regression. Results were expressed as risk ratios (RRs) (or relative differences) with 95% CIs (Supplementary Methods). The reporting of this study conforms to the TARGET guidelines (Supplement 3) [24].

A logistic regression and linear regression (hospital LOS), adjusted for confounders, was undertaken to evaluate the secondary effectiveness outcomes of prescribing and AMR, for participants who were delabeled via DOC or direct delabeling, compared with nondelabeled participants. An adjusted analysis rather than TTE was undertaken due to lack of overlap of participants eligible for direct delabel, that is, all assessed participants who could be directly delabeled were delabeled. Results were presented as odds ratios (ORs) (or relative difference in hospital LOS) with 95% CIs. Only complete case analysis was performed. Further details on analysis are provided in the Supplementary Methods.

The primary implementation outcome was reported as count, and the count per hospital was summarized as median (IQR).

RESULTS

Study Population

Between 9 November 2022 and 7 May 2025, 5121 participants underwent inpatient penicillin allergy assessment at 40 hospitals from 8 countries. The median age was 68 years (IQR, 54–79 years), 3110 (60.7%) were female, and 3888 (75.9%) were White. Baseline characteristics are in Table 1.

Effectiveness Outcomes

Primary Effectiveness Outcome: Safety of Penicillin DOC

Among 5121 participants assessed, 1573 (30.7% [95% CI, 29.5%–32.0%]) underwent penicillin DOC, of whom 1502 (95.5% [95% CI, 94.3%–96.5%]) were delabeled (Supplementary Table 4). Of 71 (4.5%) participants with a clinician-verified positive DOC, 20 (1.3%) had an immediate positive DOC and 51 (3.2%) had a delayed positive DOC. Following independent adjudication and consensus, 46 (64.8%) positive penicillin DOC events were determined to be immune-mediated reactions, 10 (21.7%) immediate IgE mediated, and 36 (78.3%) delayed-onset T-cell mediated. Of the adjudicated 46 immune-mediated positive DOC events, 24 (52.2%) had received a subsequent prolonged therapeutic penicillin course immediately post-DOC. In total, 6 (0.4%) participants had a SAE following inpatient DOC, of whom none experienced anaphylaxis. There was no mortality or intensive care unit admission following inpatient penicillin DOC (Supplementary Table 5).

Pharmacists performed most penicillin allergy assessments (54.0%), and nonallergist medical practitioners prescribed the majority of inpatient penicillin DOCs (61.3%) (Table 1 and Supplementary Table 4).

There was no significant difference in the rate of positive DOC events or SAEs when the penicillin allergy assessment was performed by different multidisciplinary clinician groups, when performed in different countries, or in different types of hospitals (Table 2). There was no difference in the rate of positive DOC events or SAEs between PEN-FAST scores (Supplementary Table 6). There was no difference in positive DOC events if immediate urticaria was reported as the phenotype (Supplementary Table 7).

Of those who did not undergo DOC (3548), 25.7% (913/3548) were directly delabeled following assessment. A total of 2415 (47.2%) participants were delabeled throughout the study period by either DOC (1502) or direct delabeling (913).

Secondary Effectiveness Outcomes: Antibiotic Prescribing and AMR—Impact of DOC

For the TTE analysis, we utilized the 5121 penicillin allergy assessments and identified 2317 (45.1%) participants with a

Table 1. Baseline Characteristics of All Participants

Characteristic	Overall (n = 5121)	Action Following Penicillin Allergy Assessment			*P* Value[a]
		DOC (n = 1573)	Direct Delabel (n = 913)	No Action (n = 2635)	
Patient characteristics					
Country					
Australia	4361 (85.2)	1398 (88.9)	793 (86.9)	2170 (82.4)	<.001
Canada	87 (1.7)	13 (0.8)	20 (2.2)	54 (2.0)	
Hong Kong	92 (1.8)	39 (2.5)	0 (0.0)	53 (2.0)	
Malaysia	130 (2.5)	9 (0.6)	45 (4.9)	76 (2.9)	
New Zealand	28 (0.5)	5 (0.3)	9 (1.0)	14 (0.5)	
South Africa	202 (3.9)	25 (1.6)	11 (1.2)	166 (6.3)	
United Kingdom	161 (3.1)	26 (1.7)	35 (3.8)	100 (3.8)	
United States	60 (1.2)	58 (3.7)	0 (0.0)	2 (0.1)	
Age, y, median (IQR)	68 (54–79)	67 (55–78)	71 (57–80)	67 (53–78)	<.001
Sex					
Female	3110 (60.7)	883 (56.1)	544 (59.6)	1683 (63.9)	<.001
Male	2006 (39.2)	687 (43.7)	369 (40.4)	950 (36.1)	
Nonbinary	2 (<1)	0 (0.0)	0 (0.0)	2 (0.1)	
Unknown (data incomplete)	3 (0.1)	3 (0.2)	0 (0.0)	0 (0.0)	
Ethnicity					
Aboriginal or Torres Strait Islander	48 (0.9)	18 (1.1)	9 (1.0)	21 (0.8)	<.001
African	36 (0.7)	9 (0.6)	4 (0.4)	23 (0.9)	
Asian	4 (0.1)	0 (0.0)	2 (0.2)	2 (0.1)	
White	3888 (75.9)	1236 (78.6)	695 (76.1)	1957 (74.3)	
Chinese	137 (2.7)	44 (2.8)	13 (1.4)	80 (3.0)	
East Asian	189 (3.7)	60 (3.8)	39 (4.3)	90 (3.4)	
Hispanic or Latino	29 (0.6)	12 (0.8)	6 (0.7)	11 (0.4)	
Indian	43 (0.8)	4 (0.3)	14 (1.5)	25 (0.9)	
Indo Asian	149 (2.9)	29 (1.8)	32 (3.5)	88 (3.3)	
Malay	38 (0.7)	0 (0.0)	17 (1.9)	21 (0.8)	
Mixed race	128 (2.5)	18 (1.1)	8 (0.9)	102 (3.9)	
NZ European	12 (0.2)	2 (0.1)	6 (0.7)	4 (0.2)	
NZ Māori	5 (0.1)	0 (0.0)	1 (0.1)	4 (0.2)	
Not Hispanic or Latino (US participants)	59 (1.2)	57 (3.6)	0 (0.0)	2 (0.1)	
Other	180 (3.5)	47 (3.0)	32 (3.5)	101 (3.8)	
Other ethnic groups, any other ethnic group	1 (<1)	0 (0.0)	1 (0.1)	0 (0.0)	
Pacific peoples	6 (0.1)	3 (0.2)	0 (0.0)	3 (0.1)	
Unknown	10 (0.2)	8 (0.5)	1 (0.1)	1 (<1)	
White, any other White background	23 (0.4)	1 (0.1)	2 (0.2)	20 (0.8)	
White, British	135 (2.6)	25 (1.6)	30 (3.3)	80 (3.0)	
White, Irish	1 (<1)	0 (0.0)	1 (0.1)	0 (0.0)	
Immunocompromised host[b]					
Yes	1552 (30.3)	473 (30.1)	252 (27.6)	827 (31.4)	.20
Unknown (data incomplete)	240 (4.7)	58 (3.7)	64 (7.0)	118 (4.5)	
CCI score, median (IQR) (if medical history form completed)	4 (2–6) (n = 4878, 95.2%)	4 (2–6) (n = 1515, 96.3%)	4 (2–6) (n = 847, 92.8%)	4 (2–6) (n = 2516, 95.5%)	.10
Pregnant					
Yes	17 (0.3)	2 (0.1)	1 (0.1)	14 (0.5)	.057
Unknown (data incomplete)	380 (7.4)	118 (7.5)	86 (9.4)	176 (6.7)	
Penicillin allergy characteristics					
Implicated antibiotic name					
Amoxicillin	624 (12.2)	180 (11.4)	132 (14.5)	312 (11.8)	<.001
Amoxicillin-clavulanate	428 (8.4)	74 (4.7)	180 (19.7)	174 (6.6)	
Ampicillin	34 (0.7)	10 (0.6)	6 (0.7)	18 (0.7)	
Benzylpenicillin	43 (0.8)	16 (1.0)	3 (0.3)	24 (0.9)	
Cloxacillin	8 (0.2)	0 (0.0)	3 (0.3)	5 (0.2)	

Table 1. Continued

Characteristic	Overall (n = 5121)	Action Following Penicillin Allergy Assessment			*P* Value[a]
		DOC (n = 1573)	Direct Delabel (n = 913)	No Action (n = 2635)	
Dicloxacillin	13 (0.3)	1 (0.1)	5 (0.5)	7 (0.3)	
Flucloxacillin	117 (2.3)	21 (1.3)	28 (3.1)	68 (2.6)	
Penicillin (unspecified)	3762 (73.5)	1252 (79.6)	542 (59.4)	1968 (74.7)	
Phenoxymethylpenicillin	44 (0.9)	14 (0.9)	11 (1.2)	19 (0.7)	
Piperacillin-tazobactam	48 (0.9)	5 (0.3)	3 (0.3)	40 (1.5)	
Time to reaction onset					
Immediate (<2 h)	1041 (20.3)	236 (15.0)	127 (13.9)	675 (25.7)	<.001
Accelerated (2–6 h)	221 (4.3)	53 (3.4)	35 (3.8)	133 (5.0)	
Delayed (7–24 h)	193 (3.8)	52 (3.3)	31 (3.4)	110 (4.2)	
Delayed (>24 h)	624 (12.2)	184 (11.7)	82 (9.0)	358 (13.6)	
Unknown	3042 (59.4)	1048 (66.6)	638 (69.9)	1356 (51.5)	
Antibiotic allergy risk assessment via NAAN App					
Very low	632 (12.3)	63 (4.0)	431 (47.2)	138 (5.2)	<.001
Low	2377 (46.4)	1102 (70.1)	280 (30.7)	995 (37.8)	
Medium	1608 (31.4)	379 (24.1)	189 (20.7)	1040 (39.5)	
High	504 (9.8)	29 (1.8)	13 (1.4)	462 (17.5)	
PEN-FAST score					
0	1314 (25.7)	641 (40.8)	181 (19.8)	492 (18.7)	<.001
1	1604 (31.3)	704 (44.8)	119 (13.0)	781 (29.6)	
2	262 (5.1)	55 (3.5)	23 (2.5)	184 (7.0)	
3	817 (16.0)	30 (1.9)	40 (4.4)	747 (28.3)	
4	29 (0.6)	2 (0.1)	3 (0.3)	24 (0.9)	
5	107 (2.1)	6 (0.4)	3 (0.3)	98 (3.7)	
NA	988 (19.3)	135 (8.6)	544 (59.6)	309 (11.7)	
Assessor role					
ID/AMS physician/consultant/attending	684 (13.4)	217 (13.8)	126 (13.8)	341 (12.9)	<.001
Allergy/immunology physician/consultant/attending	282 (5.5)	97 (6.2)	28 (3.1)	157 (6.0)	
ID/AMS registrar/fellow	307 (6.0)	120 (7.6)	59 (6.5)	128 (4.9)	
Allergy/immunology registrar/fellow	152 (3.0)	74 (4.7)	11 (1.2)	67 (2.5)	
Internal medicine/hospitalist	18 (0.4)	9 (0.6)	3 (0.3)	6 (0.2)	
Specialty registrar/fellow	67 (1.3)	30 (1.9)	26 (2.9)	11 (0.4)	
Junior medical/house officer	113 (2.2)	47 (3.0)	25 (2.7)	41 (1.6)	
Pharmacist	2767 (54.0)	829 (52.7)	559 (61.2)	1379 (52.3)	
Nurse/nurse practitioner	714 (13.9)	139 (8.8)	72 (7.9)	503 (19.1)	
Other	17 (0.3)	11 (0.7)	4 (0.4)	2 (0.1)	
Clinician intention to perform DOC at time of assessment					
Yes	1953 (38.1)	1522 (96.8)	0 (0.0)	431 (16.4)	<.001
Unknown (data incomplete)	26 (0.5)	11 (0.7)	0 (0.0)	15 (0.6)	
Reason for not proceeding to DOC					
High-risk allergy	934 (18.2)	4 (0.3)[c]	NA	930 (35.3)	<.001
Direct delabel	913 (17.8)	NA	913 (100.0)	NA	
Discharge prior to oral challenge	270 (5.3)	8 (0.5)[c]	NA	262 (9.9)	
Patient refusal	467 (9.1)	8 (0.5)[d]	NA	459 (17.4)	
Other	558 (10.9)	20 (1.3)[c]	NA	538 (20.4)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: AMS, antimicrobial stewardship; CCI, Charlson Comorbidity Index; DOC, direct oral challenge; ID, infectious diseases; IQR, interquartile range; NA, not applicable; NAAN App, National Antibiotic Allergy Network digital penicillin allergy toolkit and data collection tool; NZ, New Zealand; US, United States.

[a] *P* value from Kruskal Wallis test (continuous variables) or Fisher exact test (categorical variables).

[b] History of solid organ tumor in the past 5 years (excluding skin other than melanoma), leukemia, lymphoma, myeloma, transplant recipient, HIV, asplenia, autoimmune disease, inborn errors of immunity, or iatrogenic immunosuppression within the past 3 months. Iatrogenic immunosuppression: prednisolone >0.5 mg/kg/day for >14 days, ciclosporin, tacrolimus or sirolimus, azathioprine or mycophenolate, cyclophosphamide, leflunomide or methotrexate, monoclonal antibodies, cancer chemotherapy.

[c] Deemed inappropriate for DOC at initial assessment timepoint due to high-risk allergy, patient discharge, or patient refusal, but accepted and consented for DOC at a later timepoint or subsequent hospital admission.

[d] Declined at point of initial allergy assessment, but accepted and consented for DOC at a later timepoint.

Table 2. Safety Outcomes of Inpatient Direct Oral Challenge When Penicillin Allergy Assessment Was Performed by Multidisciplinary Clinicians, in Different Countries, and in Different Types of Health Services

Characteristic	No. of Assessments	No. DOC (% Conversion)	No. (%) Positive DOC	No. (%) Immediate Positive DOC	No. (%) Delayed Positive DOC	No. (%) SAEs[a]
Total	5121	1573 (30.7)	71 (4.5)	20 (1.3)	51 (3.2)	6 (0.4)
Type of clinician						
Allergist/immunologist	434	171 (39.4)	5 (2.9)	2 (1.2)	3 (1.8)	1 (0.6)
Nonallergist medical practitioner[b]	1205	434 (36.0)	25 (5.8)	6 (1.4)	19 (4.4)	1 (0.2)
Pharmacist	2768	829 (29.9)	37 (4.5)	11 (1.3)	26 (3.1)	4 (0.5)
Nurse/nurse practitioner	714	139 (19.5)	4 (2.9)	1 (0.7)	3 (2.2)	0 (0.0)
P value[c]	NA	<.001	.33	.94	.32	.75
Country in which penicillin allergy assessment was performed						
Australia	4361	1398 (32.1)	63 (4.5)	16 (1.1)	47 (3.4)	6 (0.4)
Canada	87	13 (14.9)	1 (7.7)	0 (0.0)	1 (7.7)	0 (0.0)
Hong Kong	92	39 (42.4)	1 (2.6)	1 (2.6)	0 (0.0)	0 (0.0)
Malaysia	130	9 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
New Zealand	28	5 (17.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
South Africa	202	25 (12.4)	1 (4.0)	1 (4.0)	0 (0.0)	0 (0.0)
United Kingdom	161	26 (16.1)	1 (3.8)	0 (0.0)	1 (3.8)	0 (0.0)
United States	60	58 (96.7)	4 (6.9)	2 (3.4)	2 (3.4)	0 (0.0)
P value[c]	NA	<.001	.95	.65	.83	>.99
Hospital peer group in which penicillin allergy assessment was performed						
Principal referral hospitals (n = 21)	4192	1303 (31.1)	58 (4.5)	18 (1.4)	40 (3.1)	5 (0.4)
Public acute group A hospitals (n = 14)	759	224 (29.5)	10 (4.5)	2 (0.9)	8 (3.6)	1 (0.4)
Other hospitals (n = 5)[d]	170	46 (27.1)	3 (6.5)	0 (0.0)	3 (6.5)	0 (0.0)
P value[c]	NA	.40	.80	.61	.41	.90

Abbreviations: DOC, direct oral challenge; SAE, serious adverse event.

[a]Includes events leading to death, a life-threatening reaction, intensive care unit admission or hospital readmission, persistent or significant disability/incapacity, or an event that requires intervention to prevent permanent impairment or damage, as adjudicated by the local clinician.

[b]Includes infectious diseases and general medicine medical practitioners.

[c]*P* value from Fisher exact test.

[d]Public acute group B, public acute group C, private acute group B, regional and remote, other acute specialized hospitals.

predefined low-risk immune-mediated penicillin allergy phenotype (PEN-FAST score <3, or "green" on the AAAT). Of the 2317 participants, 1235 (53.3%) underwent penicillin DOC. For TTE eligibility, 892 participants underwent inpatient penicillin DOC as per local protocol within the predefined window of 7 days after their allergy assessment (intervention), and 960 participants were assessed only and retained their penicillin allergy label (controls) (Figure 1).

Overall, there was a predominance of participants with a PEN-FAST score of 1 or 2 (61.7%), and index reactions other than childhood exanthem (80.0%). Participants who underwent DOC were more likely to have a microbiological diagnosis of bacterial infection (28.9% vs 13.1%, $P < .001$), be prescribed any antibiotic before penicillin allergy evaluation (74.3% vs 61.5%, $P < .001$), and be prescribed restricted antibiotics (54.1% vs 40.5%, $P < .001$) or WHO "Watch" or "Reserve" antibiotics (51.6% vs 39.5%, $P < .001$) before evaluation (Table 3).

The direct acyclic graph demonstrating the relationship between DOC and antibiotic prescribing post assessment is shown in Supplementary Figure 4. After entropy balancing was performed, groups were balanced on all baseline characteristics included (Supplementary Table 8). Weights ranged from 0.06 to 9.0.

In the weighted sample, penicillin DOC for low-risk participants was associated with a higher rate of penicillin prescribing (RR, 13.25 [95% CI, 7.82–22.46]; $P < .001$) and oral penicillin prescribing (RR, 14.62 [95% CI, 7.65–27.91]; $P < .001$) within 90 days of penicillin allergy evaluation. Participants who underwent DOC had lower rates of prescribing of restricted antibiotics (RR, 0.78 [95% CI, .63–.96]; $P = .018$) and WHO "Watch" or "Reserve" antibiotics (RR, 0.73 [95% CI, .60–.89]; $P = .002$) at 90 days post evaluation. Inpatient penicillin DOC was associated with a lower rate of acquisition of multidrug-resistant gram-negative bacteria within 90 days of evaluation (RR, 0.57 [95% CI, .33–.99]; $P = .046$) but was not associated with a difference in acquisition of other multidrug-resistant organisms, or change in LOS for the index hospital admission (Table 4 and Supplementary Table 9).

A subgroup analysis examined the effect of penicillin DOC on antibiotic prescribing based on ICH status

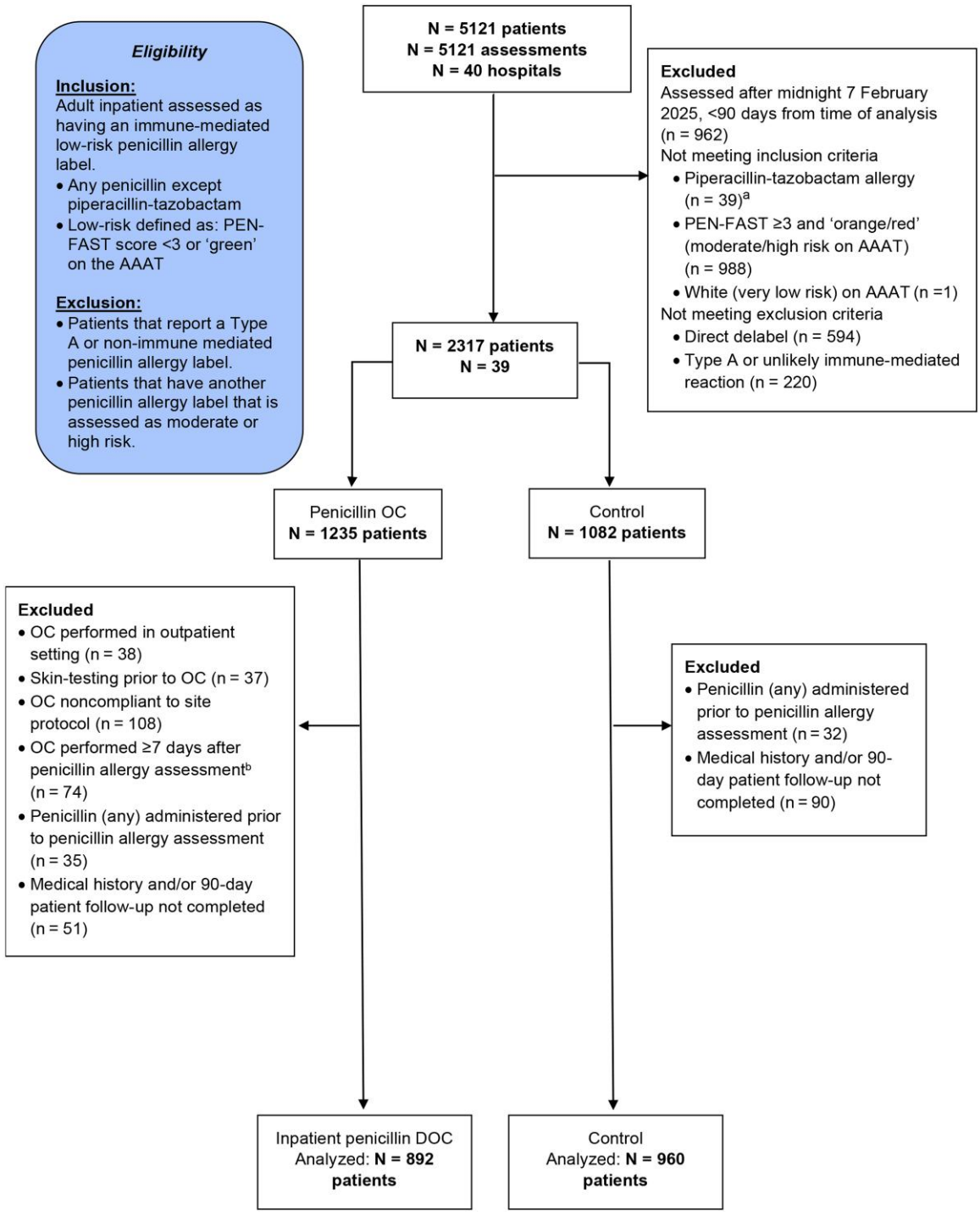

Figure 1. Target trial emulation Consolidated Standards of Reporting Trials (CONSORT) diagram. [a]Piperacillin-tazobactam excluded as oral challenge with implicated agent is not available and due to known cases of isolated piperacillin-tazobactam allergy prohibiting complete delabeling of penicillin allergy following DOC with an alternative agent. [b]Grace period of 7 days to reflect real-world practice whereby DOC may not occur immediately. Abbreviations: AAAT, antibiotic allergy assessment tool; DOC, direct oral challenge; OC, oral challenge.

(defined in Supplementary Methods) and by PEN-FAST score (Supplementary Figure 5). While both ICH and non-ICH groups demonstrated that penicillin DOC increased prescribing of penicillin within 90 days of evaluation, the effect was smaller in the ICH group compared to the non-ICH group (RR, 5.92 [95% CI, 2.96–11.83], $P < .001$ vs RR, 26.21 [95% CI, 12.17–56.41], $P < .001$; P for interaction = .005).

Table 3. Baseline Characteristics of Target Trial Emulation Participants

Characteristic	DOC (n = 892)	Control (n = 960)	*P* Value
Country			
Australia	813 (91.1)	829 (86.4)	<.001
Canada	5 (0.6)	12 (1.2)	
Malaysia	5 (0.6)	15 (1.6)	
South Africa	15 (1.7)	51 (5.3)	
United Kingdom	23 (2.6)	53 (5.5)	
United States	31 (3.5)	0 (0.0)	
Age, y, median (IQR)	68 (53.5–78)	70 (54–80)	.12
Sex			
Male	402 (45.1)	352 (36.7)	<.001
Female	489 (54.8)	607 (63.2)	
Nonbinary	0 (0.0)	1 (0.1)	
Ethnicity			
Caucasian or White	750 (84.1)	820 (85.4)	.44
Other[a]	142 (15.9)	140 (14.6)	
Immunocompromised[b]	261 (29.3)	320 (33.3)	.059
CCI score, median (IQR) (age-adjusted)	4 (2–6)	4 (2–6)	.072
Penicillin allergy characteristics			
Implicated antibiotic name			
Amoxicillin	113 (12.7)	148 (15.4)	.21
Penicillin unspecified	755 (84.6)	783 (81.6)	
Other penicillin	24 (2.7)	29 (3.0)	
Reaction type			
Childhood exanthem	208 (23.3)	161 (16.8)	<.001
Urticaria	65 (7.3)	74 (7.7)	.73
Other	619 (69.4)	725 (75.5)	
Penicillin allergy phenotype			
Unlikely immune[c]/significant	364 (40.8)	328 (34.2)	<.001
Delayed (severe and nonsevere)	360 (40.4)	383 (39.9)	
Immediate (nonsevere)	134 (15.0)	165 (17.2)	
Immediate (severe)	34 (3.8)	84 (8.8)	
Penicillin allergy risk assessment via NAAN App			
Low	712 (79.8)	653 (68.0)	<.001
Moderate/high	180 (20.2)	307 (32.0)	
PEN-FAST score[d]			
0	407 (45.6)	302 (31.5)	<.001
1	462 (51.8)	553 (57.6)	
2	23 (2.6)	105 (10.9)	
Time from hospital admission to assessment, d, median (IQR)	3 (2–7)	3 (2–6)	.10
Antibiotic and infection characteristics, preassessment			
Prescribed antibiotics preassessment			
No	229 (25.7)	370 (38.5)	<.001
Yes, infection	568 (63.7)	490 (51.0)	
Yes, surgical prophylaxis	95 (10.7)	100 (10.4)	
Specific antibiotics prescribed			
Narrow-spectrum β-lactam[e]	241 (27.0)	201 (20.9)	.002
Oral narrow-spectrum β-lactam	35 (3.9)	56 (5.8)	.057
Cephalosporin (1st or 2nd generation)	260 (29.1)	239 (24.9)	.039
Cephalosporin (3rd generation or later)	340 (38.1)	264 (27.5)	<.001
Fluoroquinolone	65 (7.3)	60 (6.2)	.37
Glycopeptide	125 (14.0)	76 (7.9)	<.001
Lincosamide	77 (8.6)	54 (5.6)	.012
Carbapenem	51 (5.7)	31 (3.2)	.009
Restricted antibiotic[f]	483 (54.1)	389 (40.5)	<.001
WHO HPCIA[g]	383 (42.9)	310 (32.3)	<.001
WHO "Watch" antibiotic[h]	458 (51.3)	379 (39.5)	<.001

Table 3. Continued

Characteristic	DOC (n = 892)	Control (n = 960)	*P* Value
WHO "Reserve" antibiotic[h]	20 (2.2)	2 (0.2)	<.001
WHO "Watch" and "Reserve" antibiotic[h]	460 (51.6)	379 (39.5)	<.001
One or more courses of intravenous antibiotics	590 (66.1)	494 (51.5)	<.001
Indication for antibiotics[i]			
Bacteremia	54 (6.1)	20 (2.1)	<.001
CNS infection	6 (0.7)	5 (0.5)	.67
Hepatitis	1 (0.1)	0 (0.0)	.30
Respiratory infection, including pneumonia	111 (12.4)	146 (15.2)	.093
Intra-abdominal infection, including gastroenteritis	103 (11.5)	106 (11.0)	.77
Infection, unknown source	24 (2.7)	31 (3.2)	.50
Skin and soft tissue, surgical prophylaxis, intravascular infection, bone and joint infection	277 (31.1)	203 (21.1)	<.001
Prophylaxis, other	18 (2.0)	31 (3.2)	.10
Urogenital infection	83 (9.3)	65 (6.8)	.044
Ear, nose, and throat infection	15 (1.7)	10 (1.0)	.23
Other infection	63 (7.1)	41 (4.3)	.009
Microbiological diagnosis			
Bacterial diagnosis	258 (28.9)	126 (13.1)	<.001
Viral diagnosis	14 (1.6)	19 (2.0)	.51
Fungal diagnosis	5 (0.6)	2 (0.2)	.22
Multidrug-resistant or *Clostridioides difficile* infection			
Vancomycin-resistant enterococci	0 (0.0)	1 (0.1)	.33
Methicillin-resistant *Staphylococcus aureus*	9 (1.0)	2 (0.2)	.025
Multidrug-resistant gram-negative bacteria	23 (2.6)	18 (1.9)	.30
Clostridioides difficile	1 (0.1)	2 (0.2)	.61
Sepsis	83 (9.3)	54 (5.6)	.003

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CCI, Charlson Comorbidity Index; CNS, central nervous system; DOC, direct oral challenge; HPCIA, highest-priority critically important antimicrobial; IQR, interquartile range; NAAN App, National Antibiotic Allergy Network digital penicillin allergy toolkit and data collection tool; WHO, World Health Organization.

[a]Includes Aboriginal or Torres Strait Islander, African, Chinese, East Asian, Hispanic or Latino, Indian, Indo Asian, Malay, mixed race, non-Hispanic or Latino, other, unknown. It is reported together due to small sample sizes.

[b]History of solid organ tumor in the past 5 years (excluding skin other than melanoma), leukemia, lymphoma, myeloma, transplant recipient, HIV, asplenia, autoimmune disease, inborn errors of immunity, or iatrogenic immunosuppression within the past 3 months. Iatrogenic immunosuppression: prednisolone >0.5 mg/kg/day for >14 days, ciclosporin, tacrolimus or sirolimus, azathioprine or mycophenolate, cyclophosphamide, leflunomide or methotrexate, monoclonal antibodies, cancer chemotherapy.

[c]Per NAAN App algorithm, "unlikely immune" encompassed unknown reactions >5 years prior and childhood exanthem.

[d]Clinical decision rule for point-of-care risk assessment of patient-reported penicillin allergy. Score ranges from 0 to 5 [17].

[e]Amoxicillin, ampicillin, benzathine penicillin, cefalothin, cefazolin, cephalexin, cloxacillin, flucloxacillin, benzylpenicillin, phenoxymethylpenicillin, pivmecillinam.

[f]Restricted antibiotics (predefined): third-generation or later cephalosporins, fluoroquinolones, glycopeptides, lincosamides, piperacillin-tazobactam, carbapenems.

[g]Third- and fourth-generation cephalosporins, fluoroquinolones, polymixins, phosphonic acid derivatives (WHO List of Medical Important Antimicrobials: a risk management tool for mitigating antimicrobial resistance due to nonhuman use, 2024. Available at: https://cdn.who.int/media/docs/default-source/gcp/who-mia-list-2024-lv.pdf.

[h]Per defined list in WHO Access, Watch, Reserve (AWaRe) classification of antibiotics for evaluation and monitoring of use, 2021. Available at: https://iris.who.int/handle/10665/345555.

[i]Some patients had >1 type of infection.

Secondary Effectiveness Outcomes: Antibiotic Prescribing and AMR—Impact of Delabeling via DOC or Direct Delabel

The impact of delabeling on antibiotic prescribing, AMR, and hospital LOS was examined in 2955 of 5121 participants who had completed 90-day follow-up by the logistic regression and linear regression analysis. Baseline characteristics of those who had follow-up completed versus those lost to follow-up are shown in Supplementary Table 10. Of 2955 participants included in the analysis, 1414 (47.9%) were delabeled via DOC or direct delabeling (Supplementary Figure 6). Delabeled and nondelabeled participants were similar with respect to age and comorbidities. The delabeled group had a higher proportion of participants with an infection diagnosis (29.6% vs 16.7%, $P < .001$) and sepsis (11.3% vs 6.2%, $P < .001$) during the index admission, and prescribing of any antibiotic pre evaluation (75.2% vs 61.6%, $P < .001$) (Supplementary Table 11).

In a model adjusting for pre assessment antibiotic use and other confounders, delabeled participants had higher prescribing of penicillin (adjusted OR [aOR], 11.7 [95% CI, 8.72–15.59]; $P < .001$), lower prescribing of restricted antibiotics (aOR, 0.67 [95% CI, .53–.85]; $P < .001$), and lower prescribing of WHO "Watch" or "Reserve" antibiotics (aOR, 0.59 [95% CI, .47–.74]; $P < .001$) at 90 days post evaluation. There was no significant increase in acquisition of multidrug-resistant or *Clostridioides difficile* infection between delabeled and nondelabeled groups (Supplementary Table 12).

Table 4. Outcomes of Target Trial Emulation Participants: Antibiotic Prescribing, Presence of Multidrug-Resistant Organism, and Hospital Length of Stay for Low-Risk Inpatients Who Underwent Direct Oral Challenge (DOC) (n = 892) Compared With Low-Risk Inpatients Who Did Not Undergo DOC (n = 960), up to 90 Days Post–Penicillin Allergy Evaluation

	Unadjusted		Weighted	
Outcome	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
Antibiotic prescribing				
Any penicillin	19.53 (12.57–30.36)	<.001	13.25 (7.82–22.46)	<.001
Oral penicillin	21.28 (12.28–36.87)	<.001	14.62 (7.65–27.91)	<.001
Narrow-spectrum β-lactam[a]	2.24 (1.82–2.75)	<.001	1.46 (1.14–1.85)	.002
Oral narrow-spectrum β-lactam	2.07 (1.60–2.68)	<.001	1.33 (.97–1.83)	.075
Cephalosporin (1st or 2nd generation)	0.62 (.49–.78)	<.001	0.46 (.36–.59)	<.001
Cephalosporin (3rd generation or later)	0.95 (.72–1.24)	.69	0.70 (.51–.96)	.026
Fluoroquinolone	1.22 (.76–1.95)	.42	0.68 (.38–1.23)	.20
Glycopeptide	0.93 (.55–1.57)	.78	0.53 (.29–.99)	.047
Lincosamide	0.57 (.32–1.05)	.070	0.38 (.20–.73)	.003
Carbapenem	0.77 (.34–1.72)	.52	0.32 (.13–.79)	.014
Any antibiotic	1.40 (1.28–1.54)	<.001	1.03 (.94–1.12)	.53
Restricted antibiotic[b]	1.11 (.92–1.33)	.28	0.78 (.63–.96)	.018
WHO HPCIA[c]	1.00 (.79–1.26)	.99	0.69 (.52–.91)	.009
WHO "Watch" antibiotic[d]	0.98 (.82–1.16)	.80	0.74 (.61–.90)	.003
WHO "Reserve" antibiotic[d]	4.30 (.92–20.23)	.064	1.84 (.39–8.65)	.44
WHO "Watch" or "Reserve" antibiotic[d]	0.97 (.81–1.15)	.72	0.73 (.60–.89)	.002
MDRO or *Clostridioides difficile* infection				
VRE	NA	NA	NA	NA
MRSA	4.30 (.92–20.23)	.064	2.75 (.59–12.93)	.20
MDRGN	1.12 (.66–1.88)	.68	0.57 (.33–.99)	.046
Clostridioides difficile	1.08 (.31–3.71)	.91	0.58 (.17–2.03)	.39
VRE/MRSA/MDRGN bacteria/*C. difficile* infection	1.27 (.81–1.98)	.30	0.66 (.41–1.06)	.083
Hospital outcomes				
Length of stay (d)[e]	1.09 (1.01–1.17)	.032	1.00 (.91–1.10)	.93

Abbreviations: CI, confidence interval; HPCIA, highest-priority critically important antimicrobial; MDRGN, multidrug-resistant gram-negative bacteria; MDRO, multidrug-resistant organism; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not applicable; RR, risk ratio; VRE, vancomycin-resistant enterococci; WHO, World Health Organization.

[a]Amoxicillin, ampicillin, benzathine penicillin, cefalothin, cefazolin, cephalexin, cloxacillin, flucloxacillin, benzylpenicillin, phenoxymethylpenicillin, pivmecillinam.

[b]Restricted antibiotics (predefined): third-generation or later cephalosporins, fluoroquinolones, glycopeptides, lincosamides, piperacillin-tazobactam, carbapenems.

[c]Third- and fourth-generation cephalosporins, fluoroquinolones, polymixins, phosphonic acid derivatives (WHO List of Medical Important Antimicrobials: a risk management tool for mitigating antimicrobial resistance due to nonhuman use, 2024. Available at: https://cdn.who.int/media/docs/default-source/gcp/who-mia-list-2024-lv.pdf.

[d]Per defined list in WHO Access, Watch, Reserve (AWaRe) classification of antibiotics for evaluation and monitoring of use, 2021. Available at: https://iris.who.int/handle/10665/345555.

[e]Results expressed as exponentiated coefficient (fold difference) with 95% CI.

Implementation Outcome

Primary Implementation Outcome: Adoption

Throughout the study period, of 242 licenses issued to clinicians, 126 clinicians utilized the NAAN App, of which 77 clinicians adopted its use within the first 6 months of site activation. The median number of users per hospital within the first 6 months was 1.5 (range, 1–5), subsequently increasing to a median of 3 users per hospital (range, 1–11) throughout the entire study period. Within the first 6 months, 20 of 40 (50%) hospitals had a single NAAN App user, 9 of 40 (22%) hospitals had 2 users, 5 of 40 (13%) hospitals had 3 users, and 6 of 40 (15%) hospitals had ≥4 users.

DISCUSSION

We undertook the largest prospective study of penicillin allergy assessment since Gadde et al in 1993 [25], and demonstrated the unequivocal safety of inpatient penicillin allergy delabeling via DOC, with inpatient participant numbers greater than and reaction rates consistent with a recent meta-analysis of heterogeneous data [26]. Implementation of multidisciplinary-led penicillin DOC, including by nonallergists, was safe and effective, congruent with previously published regional experiences [27]. This study adds weight to the growing evidence for penicillin DOC, building on RCT evidence from the ambulatory setting [9] and single-country studies in the inpatient setting [23]. Beyond just confirming safety, iNAAN also demonstrated how penicillin DOC can influence antibiotic prescribing including globally recognized antibiotics known to drive AMR.

The iNAAN study provides the largest evidence for the safety of adult inpatient penicillin DOC (ie, 95.5% negative) across a wide range of settings, including high-income and upper-middle income countries, and public, private, regional/remote,

and acute specialized hospital settings, with 17.2% of DOC occurring in nontertiary referral health services. Furthermore, iNAAN examined penicillin DOC in previously understudied populations, including the elderly (53.9% DOC participants aged >65 years) and ICH (30.1% of DOC participants). This study provides the largest single experience of inpatient penicillin DOC with real-world, pragmatic implementation of local hospital–directed DOC procedures and guidelines. Despite variations in setting, population, and local procedures, penicillin DOC was safe.

There has been increased focus on nonallergist models of inpatient penicillin allergy delabeling [28], in light of a global shortage of specialist allergists [29]. While NAAN App adoption demonstrated a median of 1.5 users per hospital within 6 months, clinical implementation of penicillin assessment and DOC was deployed by "nuclear" multidisciplinary teams, akin to the delivery of global inpatient AMS services. In iNAAN, more than half of all assessments were performed by pharmacists. Of participants assessed by pharmacists, 29.9% (827/2768) resulted in penicillin DOC, compared with 36.0% (434/1205) of nonallergist led assessments converted to penicillin DOC, with no difference in safety of penicillin DOC between disciplines. Given medical complexity and competing priorities in the acute care setting, conversion from assessment to DOC in iNAAN was consistent with other inpatient studies [10]. iNAAN provides real-world evidence that penicillin DOC can be implemented in the hospital setting by nonallergists, especially where allergy/immunology services are limited, but also where AMS programs are ideally positioned. Furthermore, this study paves the way for an increased scope of practice for pharmacists, which could help address global inequities in accessing allergy-AMS care. Increasing the capability of a multidisciplinary workforce, including pharmacists, addresses the prerequisite criteria of "human resources" for antibiotic allergy delabeling as an AMS intervention described by the WHO [30].

Although not demonstrated in RCTs [31], we utilized a TTE approach in this large prospective international dataset to examine the impact of penicillin DOC on antibiotic prescribing. Consistent with previous regional experiences, we observed a 13-fold increase in penicillin usage, 1.3-fold reduction in restricted antibiotic prescribing, and 1.4-fold reduction in WHO "Watch" or "Aware" antibiotic prescribing. While penicillin DOC did not significantly impact prescribing of restricted antibiotics or WHO "Watch" or "Reserve" antibiotics in ICH, this may be attributed to frequent guideline-directed prescribing of restricted broad-spectrum penicillin, that is, piperacillin-tazobactam, in this population. Penicillin DOC is an "enabling" intervention, moving beyond antibiotic restriction, increasing the use of penicillins as first-line antibiotic therapy. This is supported by a Cochrane review that concluded enabling interventions added to restrictive interventions have a larger immediate effect on prescribing outcomes than either intervention alone [32]. The iNAAN study demonstrated that penicillin DOC also accelerated the switch from intravenous to oral antibiotics, as recommended in international AMS guidelines [30, 33, 34].

Despite demonstrated safety and effectiveness, the implementability and sustainability of inpatient DOC has previously been ill-defined [35]. While we demonstrated adoption of the NAAN App for inpatient penicillin DOC, future research should focus on establishing whether digital point-of-care solutions can improve low-risk antibiotic allergy delabeling beyond penicillin, utilizing a similar framework of assessment for low-risk sulfonamide and cephalosporin allergies [36, 37]. The iNAAN study provides a framework for international implementation of penicillin DOC, moving beyond the evidence to practice.

Current international drug allergy guidelines indicate low certainty of evidence for penicillin DOC in adults with a distant reaction history and benign cutaneous reactions [38]. In addition to the PALACE randomized trial [9] and meta-analysis of safety data [26], this study offers high level real-world evidence, similar to a postmarketing phase 4 study, that penicillin DOC without prior skin testing is safe and effective in adults with a low-risk phenotype. International guidelines differ in their "low risk" definitions [38–40], highlighted by our recent scoping review [41]. The iNAAN data highlights that irrespective of the local definition used for low risk, and including more controversial phenotypes of urticaria (107 [94.4%] negative), penicillin DOC was safe. Global AMS policies should be updated to further increase the adoption of penicillin DOC [30].

Strengths and Limitations

This study is limited by the predominance of White participants and Australian hospitals in which penicillin allergy evaluation occurred. Regardless, inpatient penicillin allergy evaluation and DOC was implemented in 8 countries with no difference in effectiveness, including in 2 upper-middle income countries, and with 15% of participants from non-Australian hospitals. Participant hospital medical record follow-up was completed for a period of 90 days post–penicillin allergy assessment, potentially underreporting the impacts on community antibiotic prescribing. Nonetheless, we intended to examine the immediate AMS impact of penicillin DOC in the more medically complex inpatient population, many of whom were concurrently being treated for infection, rather than the healthy outpatient population. There was a considerable amount of missing antibiotic prescribing data for high-risk patients, which may have resulted in biased estimates of the overall effect of delabeling. While delabeling rates per total hospital admissions is not compared between hospitals and countries in this study, iNAAN nonetheless examined pragmatic implementation of inpatient penicillin DOC embedded within varying programs across hospitals, dependent on the available local resources.

CONCLUSIONS

This international type 2 hybrid effectiveness-implementation study demonstrated that penicillin DOC, adopted by multidisciplinary clinicians, was a safe and effective delabeling strategy for hospitalized patients with a low-risk penicillin allergy. DOC was associated with increased penicillin and reduced restricted antibiotic prescribing in the inpatient setting. iNAAN supports multidisciplinary-led penicillin DOC as a core AMS intervention for global implementation, and raises the question of whether this should be considered an inpatient standard of care and thus reflected in global AMS guidelines.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. Conceptualization: E. A. M., S. V., F. J., C. P., M. K., and J. A. T. Project administration: E. A. M., L. R. F., F. J., and I. N. Methodology: E. A. M., S. V., F. J., C. P., M. K., and J. A. T. Software: L. R. F. Investigation: E. A. M., S. B., N. P., J. P., P. H. L., A. M. C., N. A. T., R. S., M. S. M., M. R., G. M., B. J. S., P. K., D. F., M. R., R. C., K. A., A. B., A. M., A. R., A. C., Z. M.-H., C. Y., S. Cr., G. W., S. P., C. K., P. T., J. O., J. G., T. N. P., I. S., D. N., C. Ho., T. C., S. Co., C. Ha., J. W., J. B., B. L., C. D., S. L. F., and J. A. T. Data curation: E. A. M., L. R. F., S. V., and J. A. T. Supervision: C. I., J. A. R., N. E. H., S. L. F., and J. A. T. Directly accessed and validated data: E. A. M., S. V., L. R. F., and J. A. T. Formal analysis: S. V., E. A. M., and J. A. T. Writing—original draft: E. A. M., S. V., N. E. H., and J. A. T. Writing—review and editing: All authors.

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Data availability. Deidentified participant data will be available 12 months after publication upon request and approval of the proposal by the trial steering committee.

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