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Reaction Risk to Direct Penicillin Challenges
A Systematic Review and Meta-Analysis

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IMPORTANCE While direct penicillin challenges might support the expansion of penicillin allergy delabeling efforts, the perceived risk of reactions remains a key barrier.

OBJECTIVE To evaluate the frequency of reactions to direct penicillin challenges in individuals with penicillin allergy labels and to identify factors associated with such reactions.

DATA SOURCES Three electronic databases were searched (MEDLINE, Web of Science, and Scopus) from inception to July 19, 2023, for primary studies assessing patients undergoing direct penicillin challenges. Articles were included regardless of publication year, language, status, or definition of allergy risk.

STUDY SELECTION Two reviewers independently selected original studies reporting the frequency of immunologically mediated reactions following a direct penicillin challenge in patients reporting a penicillin allergy.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently extracted data and independently assessed the quality of each primary study using a risk-of-bias tool for prevalence studies.

MAIN OUTCOMES AND MEASURES The primary outcome was the frequency of reactions to direct penicillin challenges as calculated using random-effects bayesian meta-analysis of proportions. Secondary outcomes included risk factors for reactions and the frequency of severe reactions.

RESULTS A total of 56 primary studies involving 9225 participants were included. Among participants, 438 experienced reactions to direct penicillin challenges without prior testing, corresponding to an overall meta-analytic frequency of 3.5% (95% credible interval [CrI], 2.5%-4.6%). Meta-regression analyses revealed that studies performed in North America had lower rates of reaction to direct challenges (odds ratio [OR], 0.36; 95% CrI, 0.20-0.61), while studies performed in children (OR, 3.37; 95% CrI, 1.98-5.98), in outpatients (OR, 2.19; 95% CrI, 1.08-4.75), and with a graded (OR, 3.24; 95% CrI, 1.50-7.06) or prolonged (OR, 5.45; 95% CrI, 2.38-13.28) challenge had higher rates of reaction. Only 5 severe reactions (3 anaphylaxis, 1 fever with rash, and 1 acute kidney injury) were reported, none of which were fatal.

CONCLUSIONS AND RELEVANCE This systematic review and meta-analysis found that reactions to direct penicillin challenges are infrequent, with rates comparable to indirect challenges after allergy testing. These findings suggest that direct challenges are safe for incorporation into penicillin allergy evaluation efforts across age groups and clinical settings.

Supplemental content

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Inaccurate penicillin allergy labeling is a growing concern, with up to 10% of people having an unverified penicillin allergy.[1] Public health consequences of mislabeling patients with a penicillin allergy are multifold. Patients with penicillin allergy labels are more likely to be treated with second-line antibiotics, which may lead to longer hospital stays and increased health care costs.[1,2] Furthermore, the use of second-line, broader-spectrum agents has been associated with increased treatment toxicity and the development of antimicrobial resistance.[3] These factors may contribute to the increased mortality seen in individuals with penicillin allergy labels.[4] Although more than 95% of patients with penicillin allergy labels are not truly allergic, most of these patients never receive allergy evaluations.[1,2] Considering that up to 50% of inpatients are treated with antibiotics, it is crucial to increase penicillin allergy assessments and delabel those without the allergy to prevent the adverse outcomes associated with deferring first-line antibiotics.[1-3]

Many advisory and professional organizations have emphasized the need for international penicillin allergy delabeling efforts.[1] Historically, clinicians have used several approaches to evaluate patients reporting a penicillin allergy, including skin testing and graded (ie, multistep), prolonged, or single-step drug challenges. While penicillin skin testing is valuable, its sensitivity is too low to disprove penicillin allergy without a subsequent drug challenge.[5] Additionally, penicillin skin testing has a low positive predictive value, particularly in patients with low-probability pretest results.[6] Furthermore, skin tests are highly specialized and time-consuming and may take several hours or require multiple visits for evaluation.[7] Conversely, drug challenges may be the only way to assess whether an individual can safely have penicillins.

A growing body of literature supports the use of direct penicillin challenges (ie, penicillin challenge without prior skin testing) in the evaluation of penicillin allergy in patients with low-risk allergy histories.[5,7] Although not defined in the same way by all authors and entities, low-risk allergy histories frequently comprise nonanaphylactic, remote, and/or vague reaction histories. Using direct penicillin challenges may save both clinicians and patients time and associated costs in assessing for penicillin allergy.[5,8,9] Direct penicillin challenges are also a more feasible penicillin allergy diagnostic method for use by generalists, as less specialized training is needed compared with skin testing. Despite these benefits, there are drawbacks, such as hesitancy from patients, inconsistency in the definition of eligible patients at low risk, and low availability of clinics that offer direct penicillin challenges.[5,7] Importantly, perceived safety concerns may hinder enthusiasm and consensus surrounding direct penicillin challenges.[5] In this study, we assessed the safety of direct penicillin challenges for penicillin allergy delabeling across a variety of settings, risk groups, age groups, and patient populations.

Key Points

Question Are direct penicillin challenges safe for use in penicillin allergy evaluations across populations and settings?

Findings In this systematic review and meta-analysis of 56 primary studies in 9225 participants, the meta-analytic frequency of reactions to direct penicillin challenges was 3.5%. Risk factors associated with positive reactions to direct penicillin challenges included challenges performed outside of North America, in children, in outpatient settings, and with multiple dosing (graded or prolonged).

Meaning These findings suggest that reactions to direct penicillin challenges in patients with penicillin allergy histories are infrequent, occurring at similar rates to challenges performed after negative results of allergy testing.

Methods

This systematic review and meta-analysis follows the Meta-Analyses of Observational Studies in Epidemiology (MOOSE)[10] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.[11] Its protocol is registered in PROSPERO (CRD42023447566).

Eligibility Criteria

We included original studies assessing patients reporting a penicillin or β-lactam allergy (population) in which direct penicillin challenges were performed (exposure) and the frequency of reactions (outcome) reported. Patients of all age groups were included. Direct penicillin challenges (also known as direct drug provocation tests or direct oral challenges) were defined as the administration of a penicillin under strict clinical supervision without prior allergy testing, largely skin testing (eg, skin prick, intradermal) or blood testing (eg, serum-specific penicillin immunoglobulin E as used in some countries). Positive results for a direct penicillin challenge were defined as any reaction described as compatible with an immunologically mediated reaction (eg, type I IgE-mediated reactions, delayed cell-mediated reactions, or reactions caused by an immune complex[7]) following the administration of penicillin. We included cross-sectional studies and anterograde longitudinal studies (prospective or retrospective cohort studies and randomized clinical trials).

We excluded studies that performed direct challenges with drugs from another antibiotic class or that exclusively assessed patients with cephalosporin allergy. We included all eligible studies regardless of the publication language, year, status, or definition of allergy risk.

Information Sources and Search Methods

One of us (B.S.P.) searched 3 electronic bibliographic databases (MEDLINE, Web of Science, and Scopus). References of relevant studies were also reviewed. The first search was performed from database inception to April 8, 2023, with an update performed on July 19, 2023. Search queries are available in eTable 1 in Supplement 1.

Study Selection and Data Collection Process

After duplicates were removed, each study was independently assessed by teams of 2 reviewers (L.R.S., J.T.S.M., I.S., J.J.O.A., R.J.S., F.I.A.) who first screened the titles and abstracts and then read the full texts. Data were independently

extracted by the 2 reviewers using an online form purposely built for this study. A pilot version was built to assess the first 5 studies and subsequently modified accordingly. Severe reactions were defined as anaphylaxis, severe cutaneous adverse reactions, acute interstitial nephritis, serum sickness, hemolytic anemia, drug fever, reactions requiring hospitalization or epinephrine treatment, or reactions indicated by the authors as severe even if no further description was available. A full description of data extracted from each primary study is provided in the eMethods in Supplement 1.

Disagreements between reviewers were resolved by discussion with a third reviewer (K.G.B. and B.S.P.). Full texts were examined to avoid including data from the same patients more than once. If a study was written in a language unknown to us or relevant information was missing, we contacted the study's authors.

Risk-of-Bias Assessment

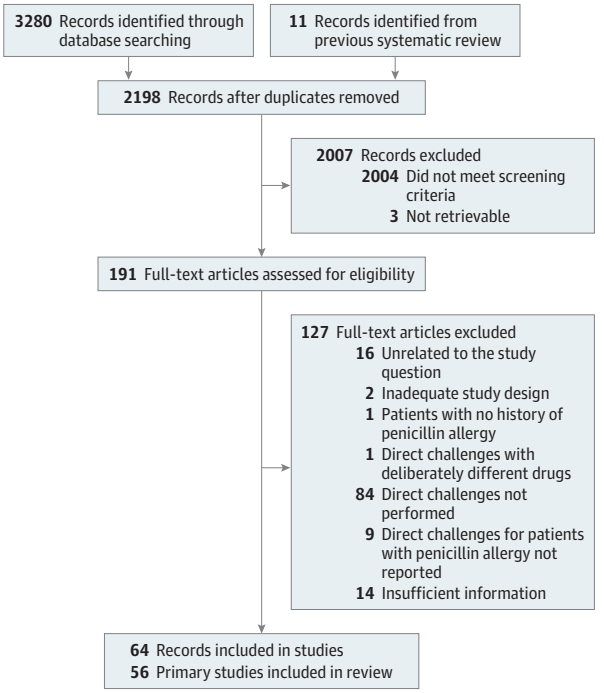
The quality of each primary study was independently assessed by teams of 2 reviewers (L.R.S., J.T.S.M., I.S., J.J.O.A., R.J.S., and F.I.A.) using an adaptation of the risk-of-bias tool developed by Hoy et al[12] for prevalence studies. Of the 11 potential items, 6 were appropriate for this study, namely if (1) the study's target population was representative of the national population, (2) the sample was representative of the target population, (3) random or consecutive selection methods were applied, (4) the likelihood of nonresponse bias was minimal (defined as <25% refusals of undergoing a direct penicillin challenge by eligible patients), (5) an acceptable or sufficiently complete definition of severe reaction was used in the study (or allergic reactions were described in detail), and (6) the same methods of assessment and data collection were used for all participants. The assessment of the certainty of evidence was performed using the Grading of Recommendations Assessment, Development, and Evaluation approach (eMethods in Supplement 1).

Statistical Analysis

We synthesized the frequency of immunologically mediated reactions and severe immunologically mediated reactions by performing a random-effects meta-analysis of log-transformed proportions. Given the scarcity of events, bayesian meta-analytic methods were applied. We assessed heterogeneity by computing an estimate of the I^2 statistic for implementation in the bayesian context. The clinical relevance of heterogeneity was assessed using methods based on decision thresholds and utilities (quantifying how frequently across the different primary studies the immunologically mediated reactions would be expected to be very small, small, moderate, or large), with best- and worst-case scenario analyses being performed. We assessed sources of heterogeneity (identifying potential risk factors for reactions) by performing subgroup analyses and meta-regression. More details are provided in the eMethods and eBox in Supplement 1.

Meta-analytic results are presented as mean values of the posterior probabilities with 95% credible intervals (CrIs). The meta-analysis was performed using the rjags package of R, version 4.3.0 (R Project for Statistical Computing).

Figure 1. PRISMA Flow Diagram of Study Selection



Results

Study Selection

The initial search yielded 3280 records (of which 1093 were duplicates) and 11 records from a previous systematic review[13] (**Figure 1**). After excluding 2004 records in the screening phase and 3 that were not retrievable, 180 records were assessed for eligibility, of which 56 primary studies (data reported in 64 records) were included in this systematic review and meta-analysis.[14-69]

Study Characteristics

A summary of the characteristics of included studies is presented in eTable 2 in Supplement 1. All studies were published between 2000 and 2023[14-69]; 25 studies were from North America (44.6%),[14,15,17,22,25-28,31,34,36,37,39,40,43,44,48,49,56,57,59,65,67-69] 18 were from Europe (32.1%),[18,19,30,32,35,45-47,50,52-55,58,60-62,66] 7 were from Oceania (12.5%),[16,23,24,41,42,63,64] 5 were from Asia (8.9%),[20,29,33,38,51] and 1 was from South America (1.8%).[21] Twenty-one studies (37.5%) analyzed exclusively children,[15,16,19-21,25,29,30,38,40,45-47,49,50,53-55,58,61,66] 21 (37.5%) analyzed adults only,[17,18,22-24,26,31,32,35,37,39,42,44,56,57,60,62,64,65,67,69] and the remaining 14 (25.0%) studied children and adults.[14,27,28,33,34,36,41,43,48,49,51,52,59,63] Most studies included only outpatients (30 [53.4%]),[14-16,19,22,26-30,33-35,38-40,44-46,48-50,52,53,55,58,60,61,65,68] or only inpatients (14 [25.0%]).[17,18,23,24,31,32,37,42,51,57,62,64,67,69] Five studies (8.9%) specifically provided data for patients reporting immediate penicillin reactions[25,27,46,49,50] (4 of which excluded anaphylaxis history[25,46,49,50]), and 11 (19.6%) provided data for patients reporting nonimmediate penicillin reactions.[19,24,25,27,46,47,49,54,55,58,66]

Only 6 studies (10.7%) performed challenges in special patient populations, including preoperative,[60] obstetrics,[44,56] Marine Corps recruits,[65] children with cystic fibrosis,[66] and critical care.[37] Prolonged challenges (multiple full doses of a penicillin taken over days [ie, a short course]) were performed in 12 studies (21.4%),[19,24,29,38,47,51,52,54,55,58,60,61] while graded challenges (1 full penicillin dose split into a partial test doses) were performed in 19 (33.9%),[17, 20, 25-27, 30, 31, 33, 34, 36, 40, 45, 48, 50, 53, 56, 57, 62, 66] and 12 (21.4%) opted for single-dose direct penicillin challenges (full penicillin dose provided in 1 instance followed by observation).[15,18,22,28,37,39,41-44,65,68] Additional direct challenge details and study protocol mapping are provided in eTable 3 and eFigure 1, respectively, in Supplement 1.

Frequency of Reactions to Direct Challenges

Of a total 9225 participants who underwent a direct penicillin challenge, 438 experienced reactions, corresponding to an overall meta-analytic frequency of 3.5% (95% CrI, 2.5%-4.6%; I^2 = 99.7%), with a frequency of 2.2% (95% CrI, 1.2%-3.2%) for adults and 6.6% (95% CrI, 4.6%-9.5%) for children (**Table 1**). Only 5 severe reactions occurred across included studies, too infrequent for meta-analysis (eTable 4 in Supplement 1). Four of these reactions were in children, including 3 instances of immediate anaphylaxis[16,20] and 1 delayed reaction characterized by fever, maculopapular rash, and elevated lymphocytes.[38] The final severe reaction was a delayed-onset acute kidney injury in an adult.[18] No fatal reactions were reported.

Subgroup Analyses

Results of all subgroup analyses are presented in Table 1. The meta-analytic frequency of reactions in North American studies (4861 participants) was 2.3% (95% CrI, 1.5%-3.1%; I^2 = 97.7%), while it was 5.9% (95% CrI, 3.4%-9.0%; I^2 = 99.1%) for European studies (3051 participants). An increase in the frequency of reactions was observed when comparing single-dose direct penicillin challenges (1.6%; 95% CrI, 0.7%-2.6%; I^2 = 77.7%; 1821 participants) with graded direct penicillin challenges (4.2%; 95% CrI, 2.3%-6.5%; I^2 = 99.2%; 4650 participants) or prolonged direct penicillin challenges (7.1%; 95% CrI, 3.5%-11.8%; I^2 = 98.3%; 1310 participants). Additionally, direct penicillin challenges performed with the suspected culprit drug had a higher frequency of reaction (4.1%; 95% CrI, 2.5%-6.5%; I^2 = 99.7%; 6382 participants) than those done with a β-lactam but not deliberately with the culprit drug (1.6%, 95% CrI, 0.7%-2.9%; I^2 = 64.7%; 879 participants). Regarding patient settings, inpatient direct penicillin challenges (n = 1356 participants) had a reaction frequency of 2.3% (95% CrI, 1.1%-3.6%; I^2 = 92.0%) compared with 4.2% (95% CrI, 2.8%-6.0%; I^2 = 99.4%) for outpatient direct penicillin challenges (4585 participants). Furthermore, direct penicillin challenges in children (5005 participants) had a reaction frequency of 6.6% (95% CrI, 4.6%-9.5%; I^2 = 99.2%), while those in adults (2053 participants) had a reaction frequency of 2.2% (95% CrI, 1.2%-3.2%; I^2 = 93.0%). Despite high heterogeneity, most studies and analyses projected a high probability of very small frequency of reactions (<52 reactions per 1000 direct penicillin challenges) even when considering worst-case scenario decision thresholds (**Figure 2**).

Factors Associated With Reaction to Direct Penicillin Challenges

Meta-regression analysis results are displayed in Table 1. We observed a lower risk of reaction to direct penicillin challenges for studies from North America (vs those of any other region; odds ratio [OR], 0.36; 95% CrI, 0.20-0.61). A higher risk of reaction was noted for studies in children (OR, 3.37; 95% CrI, 1.98-5.98), in the outpatient settings (OR, 2.19; 95% CrI, 1.08-4.75), and in studies performed using a graded (OR, 3.24; 95% CrI, 1.50-7.06) or prolonged challenge (OR, 5.45; 95% CrI, 2.38-13.25).

Follow-Up Data

A total of 15 included studies completed follow-up with participants to analyze their antibiotic use after diagnostic direct penicillin challenges.[19, 24-26, 33, 34, 37, 40, 41, 51, 54, 57, 60, 64, 69] Out of 2803 participants who were followed up prospectively, 1096 (39.1%) took a penicillin during the follow-up period. Among the 862 participants (78.6%) for whom the frequency of reactions was available, 63 reported having a reaction (3.6%; 95% CrI, 2.5%-9.4%), and no severe reactions were reported (eTable 5 in Supplement 1).

Risk of Bias and Certainty of Evidence

The risk of bias of included primary studies is summarized in **Figure 3** and eFigure 2 in Supplement 1. Of all included studies, 49 (87.5%) were found to have either a high or unclear risk of bias regarding sample representativeness.[14-16,18-34,36-47,49-52,54-58,60-62,65-69] Most included studies were found to have a low risk of bias in terms of the other parameters evaluated. Overall, 11 studies were identified to have a high risk of bias in 3 or more of the evaluated categories[15,28,32,42,46,57,60-62,67,69] (Figure 3; eFigure 2 in Supplement 1). The certainty of evidence was overall considered very low due to the observational nature of the primary studies and downgrading due to inconsistency (**Table 2**).

Discussion

Findings of this systematic review and meta-analysis suggest that direct penicillin challenges are safe for application in penicillin allergy delabeling efforts. Of 56 studies assessing the frequency of reactions following direct penicillin challenges,[14-69] reactions occurred at an estimated frequency of 3.5%, with severe reactions exceedingly rare (5 of 9225 participants, 3 instances of anaphylaxis, 1 delayed fever with rash, and 1 acute kidney injury). Direct penicillin challenges performed in North America were associated with a decreased risk of reaction compared with those performed on other continents. Additionally, direct penicillin challenges performed in children and outpatients were associated with an increased risk of reaction compared with those performed in adults and inpatients. Finally, graded or prolonged challenges showed an increased risk of reaction compared with single-dose penicillin challenges.

Table 1. Results of Univariable Meta-Regression and Subgroup Analyses for Frequency of Reactions Following Direct Penicillin Challenges

Variable	No. of studies	No. of participants (No. of reactions)	Frequency of reactions (95% CrI), %	I^2, %	OR (95% CrI)
All studies	56[14-69]	9225 (438)	3.5 (2.5-4.6)	99.7	NA
Study characteristics					
Location					
North America	25[14, 15, 17, 22, 25-28, 31, 34, 36, 37, 39, 40, 43, 44, 48, 49, 56, 57, 59, 65, 67-69]	4861 (167)	2.3 (1.5-3.1)	97.7	0.36 (0.20-0.61)[a]
Europe	18[18, 19, 30, 32, 35, 45-47, 50, 52-55, 58, 60-62, 66]	3051 (213)	5.9 (3.4-9.0)	99.1	NA
Asia or Oceania	12[16,20,23,24,29,33,38,41,42,51,63,64]	1276 (56)	4.6 (2.0-10.4)	98.7	NA
Age group					
Children (<18 y)	21[15, 16, 19-21, 25, 29, 30, 38, 40, 45-47, 49, 50, 53-55, 58, 61, 66]	5005 (315)	6.6 (4.6-9.5)	99.2	3.37 (1.98-5.98)
Adults (≥18 y)	21[17, 18, 22-24, 26, 31, 32, 35, 37, 39, 42, 44, 56, 57, 60, 62, 64, 65, 67, 69]	2053 (53)	2.2 (1.2-3.2)	93.0	1 [Reference]
Patient setting					
Outpatient	30[14-16, 19, 22, 26-30, 33-35, 38-40, 44-46, 48-50, 52, 53, 55, 58, 60, 61, 65, 68]	4585 (254)	4.2 (2.8-6.0)	99.4	2.19 (1.08-4.75)
Inpatient	14[17, 18, 23, 24, 31, 32, 37, 42, 51, 57, 62, 64, 67, 69]	1356 (37)	2.3 (1.1-3.6)	92.0	1 [Reference]
No specific participant population	50[14-36,38-43,45-55,57-59,61-64,67-69]	8405 (426)	3.9 (2.8-5.2)	99.6	NA
Penicillin direct challenge characteristics					
Challenge length					
Single dose[b]	12[15,18,22,28,37,39,41-44,65,68]	1821 (32)	1.6 (0.7-2.6)	77.7	1 [Reference]
Graded[b]	19[17, 20, 25-27, 30, 31, 33, 34, 36, 40, 45, 48, 50, 53, 56, 57, 62, 66]	4650 (257)	4.2 (2.3-6.5)	99.2	3.24 (1.50-7.06)
Prolonged[b]	12[19,24,29,38,47,51,52,54,55,58,60,61]	1310 (99)	7.1 (3.5-11.8)	98.3	5.45 (2.38-13.25)
Challenge β-lactam used					
Did not deliberately use index β-lactam	10[17,27,28,34,41,42,48,57,62,68]	879 (16)	1.6 (0.7-2.9)	64.7	1 [Reference]
Frequently used index β-lactam	9[24,26,29,47,52,56,58,63,64]	1127 (71)	5.4 (2.1-10.0)	96.3	3.35 (1.44-8.34)[c]
Used index β-lactam only	29[14-16, 19, 20, 25, 30, 31, 33, 35-40, 43, 45, 46, 49-51, 53-55, 60, 61, 65, 66, 69]	6382 (328)	4.1 (2.5-6.5)	99.7	NA
No. of drugs challenged					NA
Only 1 drug[d]	52[14-19,21,22,24-31,33-54,56-69]	8982 (408)	3.3 (2.4-4.3)	99.6	NA
Patient reaction history characteristics					
Index reaction timing					
Immediate reactions	5[25,27,46,49,50]	355 (19)	4.6 (0-67.9)	98.8	NA
Nonimmediate reactions	11[19,24,25,27,46,47,49,54,55,58,66]	2357 (144)	5.4 (1.6-12.5)	99.5	NA
Index β-lactam					
Any β-lactam	17[14, 17, 19, 29, 30, 33, 35, 41, 45, 46, 51, 54, 55, 58, 65, 66, 69]	3329 (182)	4.0 (1.9-7.4)	99.5	1 [Reference]
Any penicillin	31[15, 16, 18, 22-24, 26-28, 31, 32, 34, 36, 37, 42, 44, 47-49, 52, 53, 56, 57, 59-64, 67, 68]	3140 (121)	2.9 (1.8-4.1)	98.3	0.61 (0.32-1.19)
Aminopenicillins	8[20,21,25,38-40,43,50]	2756 (135)	5.3 (2.0-12.7)	99.2	1.29 (0.55-3.23)
PEN-FAST used?					
Yes	4[22,28,44,59]	706 (19)	3.8 (0-16.0)	81.2	0.59 (0.19-1.77)
No	51[14-21,23-27,29-31,33-69]	8503 (419)	3.7 (2.6-4.9)	99.7	1 [Reference]
Only including patients with rash history?					
Yes	6[14,25,47,48,53,61]	2542 (139)	5.7 (3.0-10.0)	82.5	1.78 (0.72-4.37)
No	49[15-24,26-31,33-46,49-52,54-60,62-69]	6667 (299)	3.3 (2.2-4.5)	99.6	1 [Reference]
Excluded if history of systemic reactions?					
Yes	22[15, 22, 25, 27, 28, 30, 31, 33, 34, 36-38, 40, 42, 48, 50, 51, 53, 59, 60, 62, 64]	5811 (294)	3.9 (2.6-5.5)	98.9	1.06 (0.58-1.97)
No	34[14, 16-21, 23, 24, 26, 29, 32, 35, 39, 41, 43-47, 49, 52, 54-58, 63, 65-69]	3414 (144)	3.2 (1.8-4.9)	99.3	1 [Reference]

(continued)

Table 1. Results of Univariable Meta-Regression and Subgroup Analyses for Frequency of Reactions Following Direct Penicillin Challenges (continued)

Variable	No. of studies	No. of participants (No. of reactions)	Frequency of reactions (95% CrI), %	I^2, %	OR (95% CrI)
Excluded if delabeled by clinical history alone?					
Yes (if possible)	8[23,24,31,42,44,48,59,63]	866 (25)	3.0 (1.5-5.2)	66.4	0.82 (0.35-1.94)
No	47[14-22, 25-30, 33-41, 43, 45-47, 49-58, 60-62, 64-69]	8343 (413)	3.6 (2.4-4.9)	99.7	1 [Reference]
Excluded based on comorbidities?[e]					
Yes	15[15, 18, 22-24, 28, 31, 38, 42, 47, 51, 55, 60, 61, 63]	1101 (61)	4.5 (2.4-7.2)	95.9	0.82 (0.36-1.90)
No	40[14, 16, 17, 19-21, 25-27, 29, 30, 33-37, 39-41, 43-46, 48-50, 52-54, 56-59, 62, 64-69]	8108 (377)	3.3 (2.2-4.6)	99.7	1 [Reference]

Abbreviations: CrI, credible interval; NA, not applicable; OR, odds ratio; PEN-FAST, penicillin allergy within past 5 years, anaphylaxis or angioedema, severe cutaneous adverse reaction, and treatment required for allergy episode.

[a] This OR is for studies performed in North America vs any other location. Of studies from North America, 16 were performed in the US[15,17,26,31,34,36,37,39,43,48,49,56,57,65,67,68] and 9 were performed in Canada.[14,22,25,27,28,40,44,59,69]

[b] Single-dose challenges are those involving the administration of a full penicillin dose in 1 instance. Graded challenges are those in which a full penicillin dose is split into a partial test dose(s). Prolonged challenges are those involving administration of multiple full doses of a penicillin taken over multiple days (ie, a short course).

[c] This OR is for studies that frequently or always challenged with the culprit drug vs those that did not.

[d] Only 2 of the included studies challenged patients with multiple drugs,[20,55] and 2 did not provide any information on the number of drugs challenged,[23,32] so meta-regression analyses were not performed for this variable (or meta-analyses for these 2 categories).

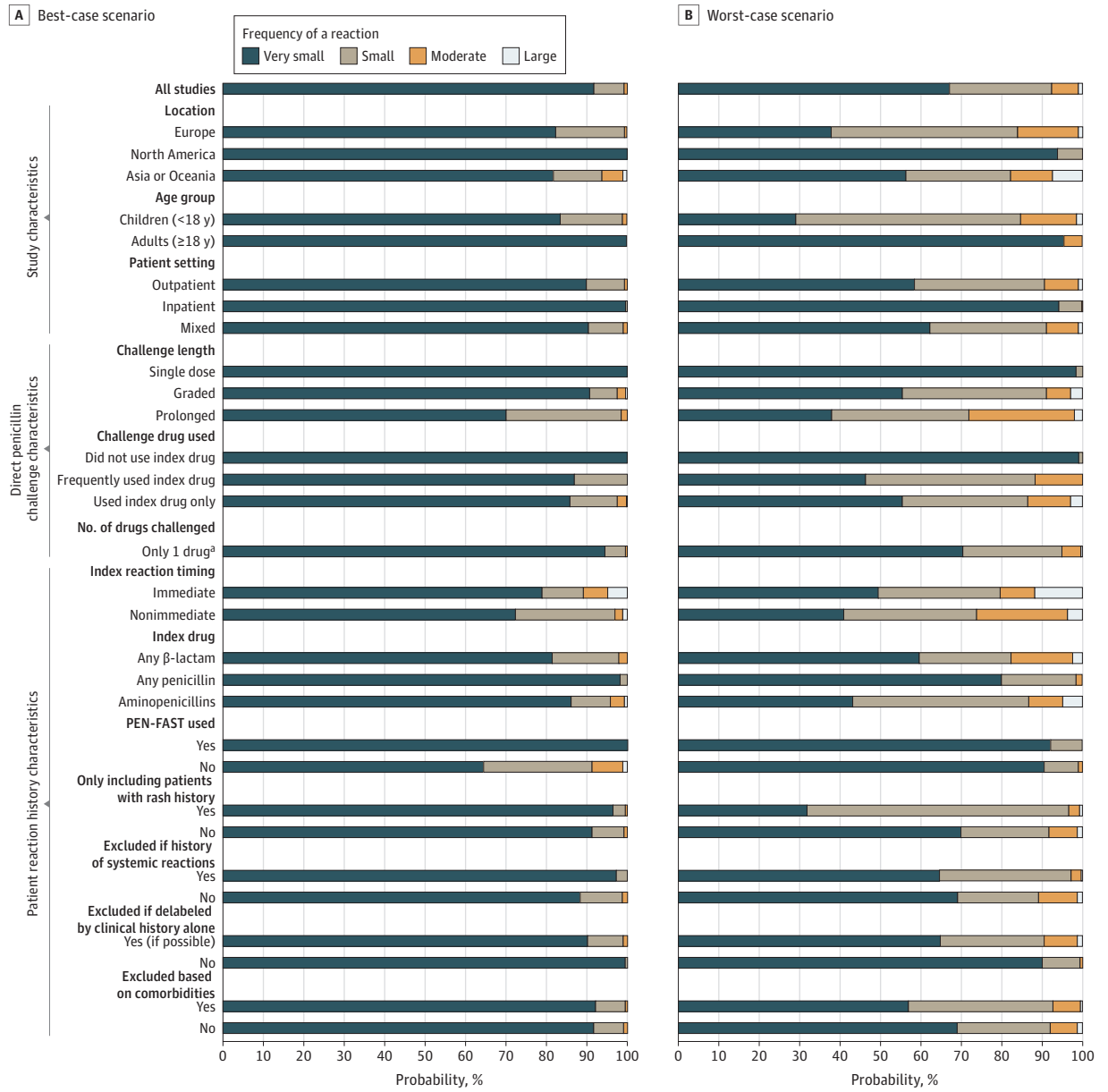
[e] The most frequent comorbidities included chronic respiratory disease (namely severe or uncontrolled asthma), cardiovascular disease, immunodeficiency or immunosuppression, and kidney or liver disease.

We found that the estimated meta-analytic frequency of reactions to direct penicillin challenges is low at 3.5% overall, 2.2% for adults, and 6.6% for children. A meta-analysis on direct penicillin challenges found a similar reaction frequency of 3.4% in adults only, despite fewer included primary studies and different quantitative synthesis methods.[5] The frequency of adults' reactions to direct penicillin challenges in our study is lower than that from a meta-analysis on penicillin challenges that found an indirect (ie, after negative skin test results) challenge intolerance rate of 14%.[70] Furthermore, the frequency of children's reactions to direct challenges in our study is slightly higher than that found in a study on indirect penicillin challenges in children (4.3%).[71] While testing prior to drug challenge is intended to determine those at risk for reactions, and despite differences in eligibility criteria, our results suggest that the overall rates of reaction to penicillin challenges are not higher than those observed when these initial tests are performed. Thus, for patients such as those included in the 56 primary studies we examined, direct penicillin challenges may be safe. Still, it is important to note that generally low-risk patients were offered direct penicillin challenges and may account for the observed lower rate of reactions to direct challenges compared with indirect challenges, which may be performed in higher-risk patients. It is also essential to highlight that we found a higher frequency of reaction to direct penicillin challenges in children compared with adults, which is notable given differing guideline recommendations for children and adults, with direct penicillin challenges indicated for pediatric patients with a history of benign cutaneous reactions but only for certain low-risk adults with distant reaction histories.[7] Therefore, compared with adults (who may more often be offered a skin test first), a higher proportion of children with actual immunologically mediated reactions may undergo a direct challenge.

We found no substantial differences in reaction rates based on differing inclusion and exclusion criteria of primary studies, indicating that even with varying criteria and risk assessments, direct penicillin challenges may be associated with consistently low rates of positive reactions. In studies performed in North America,[14,15,17,22,25-28,31,34,36,37,39,40,43,44,48,49,56,57,59,65,67-69] however, we observed a lower risk of reaction compared with studies from all other included regions (Europe,[18,19,30,32,35,45-47,50,52-55,58,60-62,66] Oceania,[16,23,24,41,42,63,64] Asia,[20,29,33,38,51] and South America[21]), supporting results from another meta-analysis on severe reactions to direct penicillin challenges.[13] This difference may be partially explained by North American studies selecting lower-risk patients. We also found an increased risk of reaction to direct penicillin challenges in outpatient settings, supporting results from another meta-analysis.[70] This finding was surprising given that inpatients might have an active infection and be at risk of nonspecific reactions or drug-infection interactions.[72] Additional studies are necessary to determine the mediators of the differing reaction rates between settings. We also observed an increase in the frequency and risk of reactions to direct penicillin challenges from a single dose to a graded dose to a prolonged challenge (1.6% to 4.2% to 7.1%). This finding suggests that clinicians may be selecting higher-risk patients for multidose (graded or prolonged) challenges, which may pick up at least 2.9% more reactions than single-dose challenges. Recent guidelines recommend against prolonged challenges,[7] but further studies are needed to understand differences between challenges with different dosing and lengths. Interestingly, our study confirmed a more than 3-fold higher reaction risk when frequently or always performing challenges to the culprit penicillin rather than another β-lactam, consistent with current knowledge on the low to negligible cross-reactivity risk among β-lactams.[7]

There are many potential benefits of incorporating direct challenges for penicillin allergy evaluation. First, the use of direct challenges may support penicillin allergy delabeling efforts, which are necessary to mitigate the adverse outcomes

Figure 2. Probability of Direct Penicillin Challenges Resulting in Very Small, Small, Moderate, or Large Frequency of Reactions



Reference values expressed as number of events per 1000 tests. PEN-FAST indicates penicillin allergy within past 5 years, anaphylaxis or angioedema, severe cutaneous adverse reaction, and treatment required for allergy episode.

[a]Only 2 of the included studies[20,55] challenged patients with multiple drugs, so subgroup analyses were not performed on this variable.

associated with penicillin allergy labels.[4] Second, while traditional allergy diagnostic tests might improve care and save costs and time, direct penicillin challenges may be even less time-consuming and resource intensive.[8,9,73] Finally, direct challenges require less allergy specialist knowledge and skill, supporting the extension of penicillin allergy delabeling efforts beyond the specialist setting, which may be necessary due to limited drug allergy services.[74] The incorporation of direct challenges as the criterion standard of penicillin allergy evaluation may improve delabeling efforts in multiple ways for patients and clinics.[1]

Strengths and Limitations

A strength of this study is the use of bayesian methods for meta-analysis of rare events. The advantage of bayesian meta-analysis compared with frequentist methods is that it adequately manages zero-cell data, which applies to many of the included studies here in which no reactions occurred. The use of frequentist methods may have resulted in an overestimation of the frequency of reaction to direct penicillin challenges.[75] Another strength of this study is that we performed meta-regression and subgroup analyses to identify patient or challenge characteristics associated with differences

Figure 3. Risk of Bias for Included Primary Studies

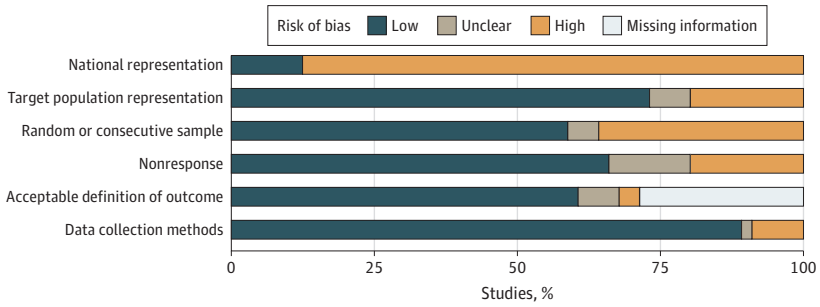


Table 2. Assessment of the Certainty in the Body of Evidence Using the Grading of Recommendations Assessment, Development, and Evaluation Approach

Certainty assessment							Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of reactions (No. of patients)	Relative, % (95% CrI)	Absolute (95% CrI)	Certainty
Frequency of positive reactions to direct penicillin challenges										
56[14-69]	Observational studies	Not serious	Serious[a]	Not serious	Not serious	None	438 (9225)	3.5 (2.5-4.6)	35 More per 1000 (from 25 more to 46 more)	Very low

Abbreviation: CrI, credible interval.

[a] High statistical heterogeneity, even though from a clinical point of view, results from the studies were mostly considered to represent trivial effect sizes.

in reaction frequencies. Finally, we used a broad query across 3 bibliographic databases and did not exclude studies based on the publication date, language, or participants' age, allowing us to capture a diverse set of studies that performed direct penicillin challenges.

This study has limitations related to the characteristics of the included primary studies. First, most studies excluded participants with severe index reactions, which may have resulted in an underestimation of the frequency of reaction to direct penicillin challenges in the general population. However, in usual clinical practice, patients with a history of severe index reactions are not typically identified for delabeling or offered penicillin challenges. Second, the primary studies largely used different definitions of low risk, limiting the performance of subgroup analysis according to allergy risk group and highlighting the need to adopt more consistent international definitions of allergy risk. Third, the studies varied in their challenge protocols as aspects, such as the drug and dosing, may have influenced the number of reactions captured. Although we were able to perform separate analyses according to these variables, there may be other characteristics we were not able to consider due to lack of available information. Fourth, study procedure variability resulted in large statistical heterogeneity. However, this heterogeneity may not be too concerning as most of the studies consistently pointed to a very small frequency of reactions. Despite differences in quantitative estimates, most studies reported fewer than 52 reactions per 1000 direct penicillin challenges. Fifth, insufficient data reporting in the primary studies (eg, missing separate data for each type or timing of index reaction or for different participant demographic groups) limited our ability to draw conclusions about which subgroups may be more at risk of reacting to direct penicillin challenges. Finally, limited follow-up data were available; thus, comprehensive follow-up studies are needed to assess the outcomes of direct penicillin challenges associated with future antibiotic use and stewardship.

Conclusions

This systematic review and meta-analysis found that reactions to direct penicillin challenges may be infrequent across a variety of patient populations and protocols, suggesting that penicillin challenges may be safe for incorporation into routine penicillin allergy delabeling efforts. Risk factors associated with reactions to direct penicillin challenges in this study included challenges performed outside of North America, in children, in the outpatient setting, and with multiple doses (graded or prolonged challenges). Despite global heterogeneity in the inclusion and exclusion criteria and clinical practices for performing direct penicillin challenges, the primary studies indicated consistently low rates of reaction and that reactions were rarely severe. Furthermore, the frequency of reactions to direct penicillin challenges in this study is similar to that shown with indirect challenges, supporting the safety of direct challenge approaches in expanding penicillin allergy delabeling.

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