Sex- and-Gender-Based Analyses of Penicillin Allergy Labels, Outcomes, and Delabeling Interventions

by
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Statement of Contributions

Mira Maximos was the sole author for Chapters 1 and 6 which were written under the supervision of Dr. John-Michael Gamble and were not written for publication. This thesis consists, in part, of five manuscripts written for publication. Exceptions to sole authorship of material are as follows:

Research presented in Chapters 2, 3, 4, 5, and appendix A: This research was conducted at the University of Waterloo by Mira Maximos under the supervision of Dr. John-Michael Gamble. The co-authors for each manuscript are listed in the citations, along with licensing details and specific contributions of Mira Maximos.

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Conceptualization: Led development of the review framework and analytic plan for the systematic review and meta-analysis.
Methodology: Co-developed review methods, eligibility criteria, and systematic review design.
Data extraction and synthesis: Oversaw comprehensive literature searches and guided study screening with co-reviewers.
Data analysis: Led synthesis and interpretation of meta-analytic results, including sex- and gender-related reporting where available.
Manuscript preparation: Led the initial manuscript draft and structured presentation of results.
Critical revision: Integrated co-author and peer reviewer feedback on final manuscript version.
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Conceptualization: Formulated the research questions and objectives for the analysis.

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Data analysis: Interpreted descriptive findings including reaction frequencies and predictors.

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Abstract

Background: Penicillin allergy labels (PALs) affect approximately 10% of the population, yet over 95% of labeled individuals tolerate penicillin following delabeling interventions. For patients who are considered low risk, oral challenge (OC) and direct delabeling (DD) are increasingly favored over penicillin skin testing (PST), although definitions of low risk vary. Sex-based differences in PAL prevalence and clinical characteristics remain poorly defined. Females are more frequently labeled with penicillin allergy and receive antibiotics more often than males, yet sex-based differences in PAL prevalence, delabeling outcomes, and antibiotic utilization practices remain poorly characterized. A clearer understanding of how sex influences PAL reporting, delabeling strategies, and antibiotic selection is needed to optimize allergy evaluation and antimicrobial stewardship.

Objectives: This thesis examined sex-based differences in PAL, delabeling strategies, and antibiotic utilization. A systematic review and meta-analysis evaluated effectiveness and safety of DD and OC in low-risk patients and assessed sex and gender differences in reporting and outcomes. A descriptive analysis characterized OC protocols, hypersensitivity reactions, and reported predictors of adverse events. A cross-sectional study assessed associations between sex and PAL in an ambulatory care hospital in Ontario, including differences in β-lactam allergy reporting, reaction severity, and comorbidities. Finally, a cohort study evaluated whether sex modifies the association between PAL and antibiotic prescribing, including antibiotic class selection and use of second-line agents when β-lactams are indicated.

Methods: This thesis is based on research utilizing multiple diverse study designs, including a systematic review and meta-analysis, a descriptive epidemiologic analysis, and cross-sectional and cohort studies. A PRISMA-guided quantitative systematic review was conducted through February 2024 to identify studies evaluating direct delabeling (DD) or oral challenge (OC) in low-risk patients compared with no intervention, penicillin skin testing, or alternative strategies. Study quality was independently assessed by two reviewers. Random-effects meta-analyses were performed, with subgroup analyses conducted in the presence of substantial heterogeneity (I^2 >75%), and qualitative data were synthesized narratively. Data from included OC studies were further analyzed descriptively to characterize challenge protocols, adverse reactions, and reported predictors of hypersensitivity, with reactions classified by timing and pooled adverse event rates estimated using random-effects models. A STROBE-guided cross-sectional study of adults

attending an ambulatory urgent medicine clinic in Ontario (2015–2024) examined associations between sex and penicillin allergy labels (PALs) using multivariable logistic regression. A retrospective cohort study of the same population assessed whether sex modified the association between PAL status and antibiotic prescribing, including antibiotic class selection and β-lactam use when indicated, using multivariable logistic regression with interaction terms; Firth's bias-reduced methods were applied when separation occurred.

Results: Across 28 studies included in the systematic review and meta-analysis (2 randomized trials, 26 quasi-experimental), sex was reported in 86%, with females comprising 61% of participants; however, only 18% disaggregated outcomes by sex and no studies reported gender variables. OC was similarly effective to PST in randomized trials (RR 1.04, 95% CI 0.95–1.13), while quasi-experimental studies reported high delabeling rates for OC (~90%). Direct delabeling was possible in approximately 27% of those included with a study arm for DD. A descriptive epidemiologic analysis of 26 OC studies demonstrated a pooled reaction or non-delabeling rate of 4% (95% CI 3–6%), most commonly mild cutaneous reactions, with higher baseline allergy burden and shorter intervals since index reaction being identified as potential risk factors. In a cross-sectional study of 29,645 ambulatory care patients in Ontario, 9.4% had a penicillin allergy label (PAL), most of which were low risk; females were significantly more likely to have a PAL than males, report multiple medication allergies, and demonstrate sex-specific associations between PAL and comorbidities. In multivariable analysis, female sex, atopic disease, older age, and number of other medication allergies were independently associated with PAL. In the cohort study, PAL was independently associated with increased antibiotic use, while female sex was associated with lower odds of antibiotic prescribing. Effect modification by sex was not detected between PAL and antibiotic use, class selection, or guideline-recommended therapy.

Conclusion: PALs remain common and are disproportionately reported among females, despite high tolerability of penicillin following evaluation. Low-risk delabeling strategies, particularly OC, are safe and effective, yet sex- and gender-disaggregated outcomes are infrequently reported limiting understanding of clinical implications. Although female sex was independently associated with PAL and distinct comorbidity patterns, sex did not modify the relationship between PALs and antibiotic utilization. These findings highlight persistent gaps in sex- and gender-sensitive evidence across the management of patients presenting with infections that have a PAL.

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List of Abbreviations

Terminology	Abbreviation
Adverse Drug Reaction	ADR
Beta-lactam antibiotics	β-lactam antibiotics
Canadian Institutes of Health Research	CIHR
Clostridioides difficile	*C. difficile*
Direct Delabeling	DD
Effective Public Health Practice Project Quality Assessment Tool	EPHPP Quality Assessment Tool
Electronic medical record	EMR
Methicillin-resistant S*taphylococcus aureus*	MRSA
Multidrug resistant organism	MDRO
Oral Challenge	OC
Penicillin Allergy Label	PAL
Penicillin-binding proteins	PBPs
Penicillin Skin Testing	PST
Place of residence, race/ethnicity/culture, language, occupation, gender/sex, religion, education, socioeconomic status, and social capital	PROGRESS
Serum specific immunoglobulin E testing	sIgE testing
Sex-and-gender based analysis	SGBA
Vancomycin resistant *Enterococcus*	VRE

Chapter 1 : Introduction and Background

Introduction

Beta-lactam (β-lactam) antibiotics, including penicillins, are bactericidal antibiotics that disrupt peptidoglycan synthesis by binding to penicillin-binding proteins (PBPs) in bacteria (1,2) and are essential first-line treatments for various infections due to effectiveness and tolerability (3–6). However, approximately 10% of the general population carries a penicillin allergy label (PAL) (7) with some literature suggesting that this may reach 15% in some subpopulations (8). This makes a PAL the most commonly reported drug allergy, (9,10) meriting further study and evaluation to better understand predictors associated with labeling and outcomes that accompany the label's presence. From a public health perspective, the high prevalence of PALs represents a substantial and modifiable burden on often broader spectrum and less well tolerated antimicrobials, given that many of these labels are inaccurate and contribute to widespread deviations from optimal antibiotic prescribing practices.

These drug allergy labels lead to the addition of flags on patient profiles that are often assumed to represent severe hypersensitivity reaction and may result in the use of second-line antibiotics, which has been associated with higher rates of hospital-acquired infections, longer hospital stays, increased costs, and greater toxicity risks (7,11–14). Other adverse outcomes include the risk of drug-resistant infections such as higher rates of hospital acquired infections including methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridioides difficile* (*C. difficile*) and vancomycin resistant *Enterococcus* (VRE) infections (7), which can adversely impact patient care and outcomes. At a population level, the presence of these multidrug resistant organisms may contribute to antimicrobial resistance, a key global public health priority, by driving the use of broader-spectrum agents and reducing the effectiveness of common first-line therapies. However, various studies have demonstrated that with appropriate assessment and allergy testing, more than 90% of individuals with a PAL can be safely delabeled using a variety of different interventions (15–18), which have been cited in literature syntheses (19,20) and clinical practice guidelines on penicillin allergy delabeling (7,21). This highlights a critical opportunity for interventions that may be conducted on a system level to improve antimicrobial stewardship, reduce healthcare utilization secondary to suboptimal antibiotic selection, and enhance patient safety through targeted delabeling initiatives.

Given that PALs are among the most common drug allergy labels and have profound implications for antimicrobial stewardship and patient outcomes, accurate assessment and management of PALs is critical. Although most individuals with a PAL can safely tolerate penicillin after evaluation, inaccurate or unverified labels continue to drive avoidable use of broader-spectrum antibiotics and contribute to

suboptimal care. Various delabeling strategies including risk stratification approaches to allow for direct delabeling without further evaluation and oral challenge with single doses of agents such as penicillin or amoxicillin offer effective solutions for patients at low risk of true allergy; however, substantial variation in their implementation and limited consideration of sex- and gender-related differences persist.

Understanding the association between PAL status and sex is merited as the majority of individuals (approximately 70%) with a PAL appear to be female (22,23); however, it is unclear if this association persists for true hypersensitivities or this could be gendered labeling without true correlation with hypersensitivity risk. Knowledge of potential predictors of PAL presence and implications on outcomes associated with the label are essential for reducing inequities, optimizing antibiotic prescribing, and informing scalable, evidence-based approaches to allergy assessment.

Impact of Penicillin Allergy Label (PAL) Presence on Patient Outcomes

The presence of a PAL on a patient's record has been associated with a myriad of negative patient care outcomes such as increased risk of adverse drug effects, therapeutic failure (7,24,25), infections with resistant pathogens, and *C. difficile* infections (7,21,26) as described throughout this thesis introduction. There are also consequent impacts on both direct patient care and healthcare system-related burden in the form of prolonged hospitalizations (27,28), and increased costs of therapeutic agents (29). Herein, studies describing the impact of a PAL on patient care outcomes will be discussed to highlight the importance of this proposed project on a myriad of patient and healthcare system factors. These studies highlight the impact of PAL presence on antimicrobial use, antimicrobial stewardship, and infection management as a general practice and therefore provide opportunities to act in alignment with the World Health Organization (WHO) strategic priorities on antimicrobial resistance to preserve antimicrobials for today and tomorrow (30).

Length of Stay

Multiple studies and systematic reviews have evaluated the impact of PALs on hospital length of stay. In a cohort study of hospitalized patients in South Carolina, individuals with a reported penicillin allergy experienced an average increase of 0.59 hospital days (95% CI 0.47–0.71) during the follow-up period compared with controls (28). Similarly, a large retrospective study from Imperial College London

analyzed data on age, sex, comorbidities, infectious diagnoses, antimicrobial use, length of stay, and penicillin allergy status and found that amongst the 38,816 patients admitted and treated with antibiotics, 14.3% had a PAL. Of the 15.8% requiring antimicrobial therapy, those with a penicillin allergy were more likely to be older, female, and have multiple comorbidities, and experienced a 5.5% longer hospital stay compared with patients without a reported allergy (31). In contrast, a study conducted at a Canadian tertiary care hospital found that while an antibiotic allergy label was initially associated with a significantly reduced daily likelihood of discharge after controlling for antibiotic administration, this association was no longer observed after adjustment for additional confounders and factors influencing discharge, resulting in no overall association between antibiotic allergy labels and length of stay (27). These studies describe the conflicting data that is present on the association between length of stay and presence of a PAL across various populations and highlight the implications of PAL on various patient-related outcomes.

Cost of Therapy

A study from the UK found that antimicrobial costs were 38.4% higher for patients with a PAL versus those without, with year-over-year increases and cost distributions skewed by a small number of patients incurring the highest antibiotic expenditures (31). In Canada, the BC Women's Hospital and Health Centre started a 'Drop the Label' campaign (32) focused on penicillin allergy delabeling in 2021 citing a 2018 pediatric study by Norton and colleagues which demonstrated that more expensive, less effective and less tolerated therapies were used in those with erroneous allergy labels (33). Although cost analyses specifically examining self-reported penicillin allergy in the Canadian context are lacking, a systematic review of available evidence on this topic published in 2018 found a direct cost associated with penicillin allergy presence of $609 in the inpatient setting and between $14 to $193 in the outpatient setting and the total inpatient cost was less for patients without a penicillin allergy by an average of between $1,145 to $4,254 per patient (costs were adjusted to 2017 United States consumer price index for inflation by the authors) (34).

Use of Second-Line Antimicrobials

In a retrospective cohort study of UK hospital patients receiving systemic antibacterial therapy, penicillins were the most commonly prescribed antibiotics among patients without a penicillin allergy (70%), whereas aminoglycosides were most frequently used in patients with a penicillin allergy (approximately 40% of those presenting with infection) (31). Other antimicrobials, including metronidazole

and cephalosporins, were more commonly prescribed in patients without a PAL, while those with a PAL most often received clindamycin, carbapenems, glycopeptides, macrolides, quinolones, and tetracyclines (31). Furthermore, a multicenter prospective Canadian cohort study of 507 hospitalized patients seen by infectious disease clinicians (2014–2015) found that among the 19% that reported a β-lactam allergy, β-lactams would have been the preferred therapy in 76% of cases (35). Among patients for whom β-lactam therapy was the optimal antimicrobial choice, 35% did not receive it because of a reported allergy despite 52% reporting non-severe reactions. Furthermore, those who did not receive a β-lactam had a significantly higher risk of adverse events (adjusted OR 3.1) (35). Across these studies it is evident that a reported PAL is associated with altered prescribing patterns characterized by frequent use of second line and more broad-spectrum agents.

Multidrug Resistant Organisms (MDROs) and Clostridioides difficile (C. difficile)

For those with a documented PAL, the resultant use of broad-spectrum and second-line antimicrobials has been linked to increased rates of *C. difficile,* MRSA, and VRE infections (7,12). Reported β-lactam allergies can be found in approximately 10% of the population (36,37) and can lead to unnecessary use of second-line antimicrobial therapy that can be clinically inferior as is seen with use of vancomycin versus a β-lactam for treatment of methicillin-sensitive *Staphylococcus aureus* (MSSA) bloodstream infections (38) and other sequalae such as increased risk of *C. difficle* infection, potentially correlated with worse clinical outcomes for hospitalized patients and prolonged length of stay (7,39). In a study of hospitalized patients with PAL in comparison to those without, it was found that those with a PAL had 23.4% higher rates of *C. difficile*, 14.1% higher rates of MRSA, and 30.1% higher rates of VRE than the control subjects (28). Another population based matched cohort study of a UK population in general practice without previous MRSA or *C. difficile* infection found that documented PAL was associated with an increased risk of both MRSA and *C. difficile*, which was thought to be mediated by β-lactam alternatives (40). In this study, increased use of alternatives to β-lactams was associated with a 55% increased risk of MRSA and 35% increased risk of *C. difficile* (40). These studies are amongst many that describe potential correlation with the presence of MDROs and increased rates of *C. difficile* in those with a PAL in comparison to those without, further stressing the importance of assessing the appropriateness of allergy labels.

Resolution and Recurrence of Infection

In a retrospective cohort study conducted at Massachusetts General Hospital surgery departments, a reported PAL was associated with 50% increased odds of surgical site infection attributed to the use of second-line perioperative antibiotics (41). Patients with a reported penicillin allergy received less cefazolin (12% versus 92%) and more clindamycin (49% versus 3%), vancomycin (35% versus 3%), and gentamicin (24% versus 3%) than those without (41). Another retrospective cohort study including all patients admitted to Veterans Affairs Hospitals in the US with a positive blood culture for MSSA found that patients who received a β-lactam had similar mortality compared to those who received vancomycin; however, those who received a β-lactam for definitive therapy had 35% lower mortality versus those who received vancomycin, with the hazard for mortality decreasing even further for those who received cefazolin or an anti-staphylococcal penicillin compared to vancomycin (38). The improved efficacy and reduced mortality with the use of an anti-staphylococcal β-lactam versus vancomycin was replicated in other studies with evidence supporting penicillin-allergy assessment strategies as ways to address the use of second-line antimicrobials for MSSA when a penicillin allergy is reported (35,41,42). These studies further describe clinically significant outcomes that are implicated in patient care when PALs are present and represent the cascade of clinical factors that can be impacted by the allergy label's presence.

β-lactam Hypersensitivity and Cross-Reactivity

Classification System for Drug Hypersensitivity Reactions

The definition of a drug allergy is an abnormal or unintended reaction to a drug in a sensitized person either in an immediate or delayed time to onset with variable immunologic mechanisms and responses (43,44). Reactions to antimicrobials often fit into a classification system comprised of 4 categories, better known as the Gell and Coombs criteria (43,45):

- Type I classification is immune globulin E mediated (IgE) with an onset of reaction occurring within 1 hour of drug administration and commonly expressed with angioedema, anaphylaxis, rhinitis, or urticaria (43,45)

- Type II classification is denoted by cytotoxic reactions that take days to manifest as potentially hemolysis or autoimmune thrombocytopenia and destruction of the host cells through formation of cytotoxic antibodies (43,45)
- Type III classification includes the formation of immune complexes days to weeks after drug exposure and results in manifestations of serum sickness, tissue injury or Stevens Johnson Syndrome (SJS) (43,45)
- Type IV classifications are delayed T-cell mediated reactions that can take a few days to manifest and often present with dermatologic manifestations such as contact dermatitis or bullous exanthems (43,45)

Some allergic reactions do not fit into one of the classification systems described above and can often be termed idiosyncratic (45) with hepatic drug reactions (whether cholestatic or hepatocellular) and some interstitial lung disease reactions being described as idiosyncratic events (43).

Antimicrobials can result in adverse drug reactions (ADRs) or hypersensitivity reactions through a multitude of mechanisms with hypersensitivity reactions making up between 10% to 20% of all ADRs (43,46). Of the different reactions, cutaneous manifestations including rash and hives are the most commonly reported with β-lactams in particular; however, the challenge arises in the lack of validation of the diagnosis of antimicrobial hypersensitivity reactions from other causes such as rashes associated with viral infections or bacterial infections such as *Streptococcus pyogenes* (46).

PALs are common, persist over time, and are increasingly recognized as potentially important allergy labels to validate given clinical implications, creating important opportunities for improved risk stratification and delabeling (43–45).

Penicillin Hypersensitivity Reactions

In the early 1920s with Alexander Fleming's serendipitous discovery of benzylpenicillin came an introduction of therapies used for treatment of wounds and infections that previously led to exorbitant mortality rates (1). Beta-lactams as a class are bactericidal antibiotics that bind to the penicillin-binding proteins (PBPs) of gram-positive and gram-negative bacteria resulting in disruption of peptidoglycan synthesis with different bacterial species exhibiting distinct PBPs (1,2).

Since the introduction of benzylpenicillin and the subsequent development of the β-lactam class, structural determinants such as penicillin metabolites (e.g., penicilloyl) and shared or similar side chains, rather than the β-lactam ring itself, have been shown to drive most hypersensitivity and cross-reactivity patterns across penicillins, cephalosporins, carbapenems, and aztreonam (1,45,47,48). Most often, immunogenicity to penicillin results from reaction to the metabolites. Penicilloyl, for example, has been shown to covalently bind to proteins that react with IgE antibodies and is recognized as a major determinant for penicillin hypersensitivity (45). Beta-lactam side chains may also be implicated in hypersensitivity reactions to this class of antimicrobials; all penicillins contain a beta-lactam and thiazolidine ring, with individual penicillins distinguished by their respective side chains (45,48).

Given that approximately 10% of the general population carries the label of penicillin or another β-lactam allergy (7,46,49) with some literature suggesting a prevalence of up to 15% in hospitalized patients (21), it is important to better contextualize the epidemiologic distribution of these allergies and cross-reactivity with other β-lactam agents in order to better elicit more accurate allergy histories and create delabeling approaches and toolkits. The other classes of beta-lactams to consider for cross-reactivity risk include cephalosporins, carbapenems and the monobactam, aztreonam, which are further described below.

Cephalosporin Hypersensitivity Reactions

Early reports of high penicillin–cephalosporin cross-reactivity following the introduction of cephalothin were later shown to be overestimated, with subsequent studies reporting substantially lower rates, likely due in part to early manufacturing contamination and recognition that shared side chains, rather than the β-lactam ring, drive most cross-reactivity (45,50,51).

In the 1960s when cephalothin was marketed, there were reports of anaphylactic reactions in patients with a history of penicillin allergy. These reactions prompted a literature review to better quantify the incidence of cross-reactivity, which was reported as 40%; however, latter studies failed to support this rate of cross reactivity, instead reporting rates between 0% to 10.5% (45). In the 2000s, a paradigm shift began to occur that supported the use of the majority of cephalosporins in penicillin-allergic patients (52). The results of earlier studies that overestimated the cross reactivity of cephalosporins and penicillins were hypothesized to have been impacted by contamination since penicillin-related products were produced with the use of *Cephalosporium* mold, which contained trace amounts of penicillin in the preparation (53).

During the initial period of attempting to understand the molecular rationale for cross-reactivity between penicillins and cephalosporins, there were suspicions that the β-lactam ring was the agent associated with reactions across the β-lactam classes; however, as research on β-lactam cross reactivity progressed, it became more evident that cross-reactivity was more likely due to similar side chains in the penicillins and some cephalosporins (51). Typically, cephalosporins are very well tolerated with an incidence of non-severe adverse reactions of less than 5% and severe reactions such as anaphylaxis making up less than 0.1% (45).

Carbapenem Hypersensitivity Reactions

Carbapenems share a β-lactam core with penicillins (45) but differ structurally by replacement of sulfur with carbon (54). Overall, carbapenems as a class are very well tolerated with post-marketing studies of tolerability of this class showing reactions occurring less than 5% of the time (45,55,56); however, in many of these studies, a prior history of anaphylaxis to any β-lactam was a reason for exclusion (45,54) and therefore may have predisposed the population to lower risk of reactions as a selection criterion.

In the early 2000s, some retrospective data began to emerge that better elucidated the rates of cross-reactivity between carbapenems and penicillins and demonstrated lower rates of cross-reactivity than previously reported. An example is a cohort study of 266 patients who were administered imipenem/cilastin or meropenem in a US Health System between 2001 to 2002 which found that of those with a reported penicillin allergy, 9.2% developed a hypersensitivity reaction and of those without a penicillin allergy 3.9% developed a hypersensitivity reaction with the difference not being statistically significant (57). This evidence provided support for the use of carbapenems, if clinically indicated, in patients with low-risk allergies.

Monobactam Hypersensitivity Reactions

The monobactam class is unique in that there is only one commercially available antibiotic available, namely aztreonam, with a spectrum of activity limited to non-anaerobic gram-negative microorganisms (45). Aztreonam has a monocyclic ring at its center and is completely synthetic, whereas other β-lactams are composed of a central bicyclic ring structure with varying side chains and adaptations to the central bicyclic ring structure (45). Aztreonam is often well-tolerated with drug reactions reported to occur in 2% of cases (45); however, there appears to be an increased risk of hypersensitivity in patients with cystic fibrosis upon sensitization, which may not be unique to aztreonam as an agent but more

consistent with impaired antigen exclusion at mucosal cell surfaces (58). Although aztreonam can be safely administered in patients with a history of penicillin allergy, there is a potential for cross-reactivity with ceftazidime due an identical side-chain; therefore, caution should be exercised following administration of aztreonam to a ceftazidime allergic patient (59,60).

Management of Hypersensitivity Reactions

Management of Penicillin Allergies

A series of studies have demonstrated that upon appropriate assessment and allergy testing, more than 90% of individuals with a penicillin allergy label can be safely delabeled using a variety of unique interventions (15–18) that have been cited in literature syntheses (19,20) and clinical practice guidelines on penicillin allergy delabeling (7,21). Therefore, having a framework to guide penicillin allergy assessment is essential for clinicians when approached with this common question.

There are 3 main facets for understanding penicillin allergies (24):

1. Penicillin allergies often wane in time, with half of individuals no longer having an allergy after 5 years from time of initial reaction,
2. Most reported patients can be safely delabeled of their allergies with appropriate assessment and testing, and,
3. Cross reactivity between β-lactams is less common than previously thought, which is described in the penicillin hypersensitivity reactions section above.

The first step in assessing a penicillin allergy is obtaining a detailed history; therefore, an approach to penicillin allergy assessment or testing can support successful delabeling or validation of the allergy. Penicillin allergy risk stratification can be carried out through skin testing, serum specific immunoglobulin E (sIgE) testing for β-lactam, oral challenge, and delabeling on clinical history. For this thesis, we focus on the optimal method to delabel low-risk penicillin allergies as this is the population most likely to be safely delabeled in the community without specialist evaluation.

Skin Testing

If a patient's history is suspicious for an allergic reaction, the first step is often consideration of skin testing, which comes in the form of prick or intradermal applications and is appropriate for immediate hypersensitivity reactions such as suspected anaphylaxis, angioedema, urticaria, conjunctivitis, or allergic rhinitis (61). The risk of systemic reactions is lower for skin prick testing than for intradermal testing; therefore, individuals who are often considered at higher risk of systemic and anaphylactic reactions such as those with a previous history of anaphylactic reactions, pregnant persons, and small children may benefit from this approach (61).

Historically, penicillin skin testing has been the gold standard method for confirming allergic reactions to penicillins, with a negative test demonstrating a negative predictive value of 97% to 99% and a positive predictive value of approximately 50% (45). However, another study reported different predictive values, with a positive predictive value ranging from 50% to 75% (7) and a systematic review of the literature on penicillin skin testing published in 2020 noted that, among 105 primary studies assessing over 30,000 patients, skin testing sensitivity was 30.7% (95% CI 18.9–45.9) and specificity was 96.8% (95% CI 94.2–98.3) (62).

Therefore, although PST represents a safe and reasonable method to assess allergy risk, it can overestimate risk and result in false-positive findings, leading to unnecessary avoidance of penicillin in individuals with low-risk allergies who would otherwise most likely tolerate an oral challenge if given the opportunity. Accordingly, evidence is shifting to suggest that in low-risk populations, direct oral challenge may become the primary accepted method for allergy review and delabeling (20,28,43), while in populations with moderate- or high-risk allergies, the conventional approach of PST or other methods described below continue to be considered the gold standard or optimal strategies.

Serum IgE Testing

Assays for IgE antibodies to specific allergens, particularly food and common airborne allergens are readily available (63); however, IgE antibodies for medications have less clinical utility and are considered only if skin testing is inconvenient or difficult to perform (63).

Oral Challenge (OC)

Oral challenge can be considered in the setting of delayed, non-severe reactions, such as childhood rash occurring more than 10 years prior (24). Selection of the optimal penicillin for hypersensitivity assessment can be challenging, as rare individuals may retain hypersensitivity to one penicillin (e.g., amoxicillin) while tolerating another (e.g., penicillin VK) due to differences in R1 side chains surrounding the β-lactam ring (24). Increasing evidence over the past decade supports proceeding directly to oral challenge in patients without moderate-to-severe hypersensitivity reactions, given the lower sensitivity of PST (20,62,64) and limited timely access to PST when penicillin is the preferred treatment for active infection.

Decision algorithms are useful for identifying low-risk individuals suitable for OC with a low incidence of adverse events. A 2022 study evaluating a standardized algorithm in 800 cases found that 74.4% of reported β-lactam allergies were excluded by negative challenge testing; IgE-mediated immediate reactions were diagnosed in 8.7%, and delayed hypersensitivity in 16.9% (65). Algorithm accuracy in this study was highest for moderate-to-severe Type I reactions (97.7%) compared with mild reactions (73.1%) and identified 90.4% of delayed hypersensitivity reactions (46). Overall, the algorithm enabled delabeling of approximately 50% of individuals classified as low risk but failed to identify the remaining half.

Among individuals reporting penicillin allergy, approximately half are classified as low risk depending on study-specific definitions and stratification parameters (64). However, a consistent definition of low-risk allergy remains lacking despite growing evidence supporting oral challenge for delabeling. Further refinement of low-risk criteria is therefore needed to guide safe clinical practice. Accordingly, optimizing patient selection for low-risk definitions was completed as a part of this thesis. This work complemented a 2021 systematic review by Cooper et al. evaluating the safety and efficacy of direct oral challenge in low-risk populations (20).

Direct Delabeling (DD)

Accurate allergy assessment relies on careful history taking including evaluation of reaction timing, severity, duration of symptoms, prior reactions, time since the initial reaction, and relevant comorbidities (64). Timing is critical, as immediate reactions occurring within one hour of drug exposure are more likely to be IgE mediated, whereas delayed reactions developing over hours to days are more often T-cell mediated and may persist or worsen if not appropriately managed (64).

The integumentary system is most commonly involved in drug hypersensitivity reactions and immediate reactions may initially present as urticaria alone or with high-risk features including rapid onset widespread urticaria, angioedema, anaphylaxis, wheezing, hoarseness, dyspnea, palpitations, hypotension, severe blistering rash, mucosal involvement, systemic symptoms, or respiratory arrest or collapse (64). Symptom duration and recurrence further inform reaction severity, and patients with significant comorbidities such as severe ischemic heart disease or poorly controlled pulmonary disease may be at increased risk of adverse outcomes in the setting of true hypersensitivity (64).

When history taking identifies a non–immune-mediated adverse drug reaction, such as isolated gastrointestinal symptoms, the allergy label can be safely removed from the patient's chart (24). Similarly, penicillin allergies reported solely on the basis of family history without personal exposure or reaction may be safely delabeled (24). Numerous strategies and intervention approaches have been considered for delabeling low-risk allergies, which are considered across the first objective of this thesis.

A Focus on Penicillin Allergy Delabeling Interventions in Low-Risk Patients

Despite the evidence regarding low risk of true hypersensitivity and cross-reactivities between the different β-lactams, PALs continue to influence antibiotic utilization practices, underscoring the need to examine sex-based differences in PAL prevalence, delabeling strategies and outcomes, and downstream antibiotic utilization, which are the focus of this thesis.

For PST, variability in test validity may arise from differences in true prevalence and assay methods, complicating local applicability. The low sensitivity of PST described above is particularly relevant for patients with low-risk allergy histories, as overdiagnosis of the allergy label can lead to inappropriate antimicrobial use and suboptimal outcomes. Furthermore, PST is often performed by allergists or immunologists, and referral to these specialists can take months which can delay appropriate antibiotic use if the patient is presenting with an active infection that would be amendable to treatment with a β-lactam agent.

The use of questionnaires or structured algorithms to directly delabel (DD) or oral challenge (OC) with a penicillin are becoming increasingly preferred for addressing low-risk allergies due to excellent sensitivity and tolerability of testing approaches (20) as well as the ability to apply these methods promptly prior to antibiotic initiation, when required. Although it is notable in the literature that the use of structured questionnaires to DD patients with penicillin allergy labels who are unlikely to be allergic based on a

detailed history and OC interventions are successful, there has not been a published knowledge synthesis that describes the optimal population that would be considered low risk and appropriate for this intervention with considerations for sex and gender given the notable higher prevalence of PAL in females (22,23), nor has the efficacy and safety of these interventions in low-risk participants been quantified. Therefore, addressing this gap is important to ensure that the appropriate patient population is included in these interventions.

An Overview of Relevant Predictors and Risk Factors Associated with PAL Presence

Another important consideration that appears to be lacking in the literature is the association between PAL presence and other predictors (covariates) that may be clinically relevant and influence the association between PAL presence and patient sex such as age, correlated comorbidities, intersectional factors, number of medication allergies, and severity of illness at presentation for a clinical encounter. Consideration of these factors in multivariable models can improve our understanding of the relationship between these variables and the presence of PAL.

The assessment of covariates associated with differences in patient-related outcomes by PAL status, such as antibiotic prescribing, frequency of hospital encounters, and other clinically relevant outcomes such as presence of drug-resistant pathogens, would provide further content on the impact of PAL presence on patient care and the implications to antibiotic stewardship. Therefore, inclusion of all relevant variables in multivariable models may provide a better understanding of the relationship between PAL presence and other variables that could better define which patients are more likely to have a PAL on their medical record and what this means for clinical care.

Comorbidities as Predictors of PAL Presence

The evidence pertaining to predictors of penicillin allergy in the general population is limited and is often extrapolated from knowledge about overall drug allergies. There is evidence that inflammatory conditions such as Systemic Lupus Erythematosis, Sjogren's syndrome, and adult-onset Still's disease have a higher correlation with drug allergies (66) and can therefore be assessed as predictors of penicillin allergies given the limited scope of evidence pertaining to the underlying pathogenesis of penicillin allergies in the context of all drug allergies.

Other risk factors described as potentially correlated with presence of penicillin allergy in the general population appear to be multiple allergies on a patient's profile (67), age at presentation of allergic reaction (67), type of β-lactam administered (67), atopic conditions (asthma, eczema, seasonal allergies, rhinitis) (68), obesity (69), and potential genetic polymorphisms for cytokines involved in the regulation of immediate hypersensitivity reactions (67). Furthermore, sex and gender can be risk factors for predicating differences in efficacy and safety of therapeutic alternatives (70–72) with sex associated with higher prevalence of penicillin allergy in females over males in one study of adult patients and not associated as a predictor in a study of pediatric patients (22,73).

Integration of Sex and Gender into Epidemiologic Studies Addressing PALs

For the purposes of this thesis, Sex- and Gender-Based Analysis (SGBA) terminology is used in accordance with the Canadian Institutes of Health Research (CIHR), whereby sex refers to biological attributes and their expression and gender refers to socially constructed roles, behaviours, expression, and identity (74). The concepts in this thesis that centre around sex, gender, and intersections are derived from a foundational theory on intersectionality as introduced by Kimberle Crenshaw's work (75). This framework argues that a system of oppression such as racism and sexism are not independent facts but in reality, are intersecting factors that shape unique experiences. Application of Crenshaw's work stems from a report focused on the experiences of Black women through legal and policy frameworks in ways that cannot be understood when each factor is studied or considered alone. This framing has been operationalized through various approaches that include the study of intersectionality including the PROGRESS-PLUS (76) framework and Health Canada's Canadian Institute for Gender and Health's Sex and Gender Based Analysis Plus framework (CIHR SGBA+) (74).

For the purpose of this thesis, the categories of the PROGRESS-Plus framework (Place of residence, Race/ethnicity, Occupation, Gender/sex, Religion, Education, Socioeconomic status, Social capital, plus additional factors such as age, disability, and other context-specific characteristics) are used as a structural approach to identifying intersecting determinants of health as related to PAL presence, predictors, and outcomes associated with PAL. The CIHR SGBA+ framework is used to inclusively consider sex and gender-based analysis across all studies in the thesis, where possible. The gaps associated with reporting or availability of information are described where applicable. Incorporating a sex and gender lens is increasingly important in understanding PALs as females consistently report higher rates of

penicillin allergy in adult populations, though it remains unclear whether this reflects biological sex, gendered factors in healthcare delivery, or their intersection (22,23).

Biological sex influences pharmacokinetic and pharmacodynamic processes and has been considered as a potential reason for differences in adverse drug reactions (ADRs) by sex, potentially mediated by hormonal, immune, and inflammatory differences including variation in cytokine expression, mast cell activity, histamine receptor expression, and immune cell responsiveness (70,77–80). Female propensity to drug allergy has also been hypothesized to reflect a combination of factors including social constructs such as differences in healthcare utilization and prescribing patterns, genetic factors, and hormonal influences on immune cells that may affect hypersensitivity reactions, including anaphylaxis (78,81). Female sex has been identified as a predictor of penicillin hypersensitivity in observational studies of adult patients using both PST-confirmed and self-reported data (22); however, this association was not observed in a smaller pediatric cohort (73). In one adult observational study, demographic characteristics, PST results, comorbid drug allergies, and time from index reaction were collected in a pre-operative clinic setting and analyzed using univariate logistic regression, demonstrating sex-based differences in rates of positive PST (22). In contrast, a 2011 study of 778 pediatric patients evaluated for penicillin allergy using PST did not identify sex-based differences in hypersensitivity risk (73).

Sex-based pharmacokinetic and pharmacodynamic differences may further contribute to variability in drug reactions and adverse event reporting. Studies demonstrate differences in absorption, metabolism, distribution, and elimination between sexes, with corresponding clinical differences in ADR reporting (82,83). Additional biologic factors including gastric pH, gastrointestinal motility, plasma protein binding, and metabolic enzyme activity further influence drug safety and efficacy (83). A scoping review of pharmacovigilance databases reported that females more frequently report ADRs than males (77), supporting a broader biologic basis for sex differences in drug responses. Evidence also suggests that sex assigned at birth influences the prevalence of immune-mediated hypersensitivities, including PALs, in adult populations (22,23). However, prior studies evaluating sex as a predictor of PAL often did not account for important covariates such as age, multiple medication allergies, autoimmune or atopic conditions, or metabolic comorbidities, all of which may modify hypersensitivity risk. More recent evidence incorporating these factors informs the current work.

This highlights a critical gap in understanding whether biological sex modifies the relationship between PAL and antibiotic outcomes. Investigating the association between sex and, where possible,

gender, and both the presence of a PAL and the likelihood of true penicillin hypersensitivity is essential to informing equitable clinical assessment, delabeling strategies, and antibiotic prescribing, and represents a core objective of this thesis.

Gender and Equity in Penicillin Allergy Label Reporting and Outcomes

Gender is a complex construct of roles, identities, relationships, and social factors (84). A growing body of evidence suggests that various factors unrelated to a particular disease process physiology or pathology impact both morbidity and mortality and live at the intersection of sex and gender. An example of this would be institutional gender expressed through health care professional decisions that may shape norms and expectations across social institutions and, therefore, impact diagnostic schemas at presentation and thus potentially patient outcomes (84,85). Furthermore, a term known as intersectionality, which encompasses various social, structural, and individual identity factors (86), when coupled with sex and gender, may further be implicated in differences in patient outcomes for individuals across the gender spectrum.

Although various bodies of literature describe that health equity may be impacted by sex, gender, and intersecting factors, it has been challenging to quantify the impact of these variables on patient care. Therefore, the use of surrogate markers and processes, such as the PROGRESS acronym (76), which encompasses an individual's place of residence, race, ethnicity, culture, language, occupation, gender, sex, religion, education, socioeconomic status, and social capital, may help to streamline both data collection and findings related to SGBA factors when studying health research through an equity lens.

Given that data related to SGBA in penicillin allergy risk stratification literature has been sparse, the focus of this thesis will be to describe evidence that discusses both presence and absence of sex, gender, and equity-related factors to design future interventions that consider these factors using systematic approaches that focus on understanding causal pathways for differences in patient outcomes .

Overall Aim and Objectives

To improve patient care, it is essential to better understand the prevalence of penicillin allergies in the general population, categorize these allergies into low- and high-risk groupings, and understand which type(s) of intervention (i.e., direct delabeling, oral challenge, or other approaches) are most appropriate for

subgroups of patients presenting with PALs. It is also essential to apply an intersectional lens, with a particular focus on sex assigned at birth, to better understand whether there is a true higher prevalence of penicillin allergies in women or, if after intervention both men and women have a similar rate of true penicillin allergy presence, to begin to understand the interconnected nature of social categorizations and healthcare-related outcomes. This work will help to inform the development of equitable resources for PAL assessment and understand the implications for patient outcomes, starting with understanding their prevalence and impact on antimicrobial use and recommending strategies to optimally delabel individuals with low-risk penicillin allergies.

To address these aims, this thesis is structured around three overall objectives:

- **Objective 1: To describe the characteristics of individuals with PAL, common delabeling interventions, and the effectiveness of those interventions.** Describe the population presenting with PALs, determine the proportion that would be considered low risk and describe the definitions of low risk using a series of knowledge syntheses and descriptive epidemiologic studies of published literature. The synthesis of the evidence includes effectiveness and safety of penicillin allergy delabeling interventions in low-risk patients - a target population that may be delabeled more readily in resource-limited and outpatient settings. This is followed by a descriptive epidemiologic study that further refines the types of interventions and antibiotics that are used in delabeling low risk allergies. This work is stratified by sex and, where applicable, gender- and equity-related factors.
- **Objective 2: To measure the association of sex and comorbidities with the presence of a PAL.** To better understand factors associated with PAL presence, a cross-sectional study is conducted using data from an ambulatory care hospital's electronic medical record database to measures the association between sex and the presence of a penicillin allergy label upon hospital admission. This study better defines the clinical and social factors that are interconnected with PAL presence in a large Canadian cohort of patients.
- **Objective 3: To determine if sex is an effect modifier for the association between PAL and clinically relevant outcomes.** The last study, a cohort study using data from an ambulatory care hospital's electronic medical record database, is designed to determine if sex is an effect modifier for the association between penicillin allergy label status and antibiotic utilization.

Content of Chapters

Chapter 1 provides an overview of penicillin allergy label presence, interventions to delabel penicillin allergies, and sex and gender variables that may impact patient care, describes literature surrounding penicillin hypersensitivity reactions, and describes literature that presently includes predictors of penicillin allergy label presence with a focus on sex, gender, and equity related factors. **Chapter 2** contains the first project of this thesis, which is a co-designed systematic review and meta-analysis that aims to synthesize the evidence regarding the effectiveness and safety of penicillin allergy delabeling interventions in low-risk patients with consideration for sex, gender, and equity-related factors. **Chapter 3** aims to characterize the interventions commonly used for oral challenges, classify reported reactions, and identify reported predictors of hypersensitivity reactions in randomized controlled trials and quasi-experimental studies involving an oral challenge for patients with low-risk penicillin allergies. **Chapter 4** describes a cross-sectional study that measures the association between sex and the presence of a penicillin allergy label upon hospital encounter. **Chapter 5** describes a cohort study designed to determine if sex is an effect modifier for the association between penicillin allergy label status and antimicrobial treatment and outcomes. **Chapter 6** summarizes and discusses the various works included in this thesis, lists and describes future directions and clinical implications of this work

Chapter 2 : A Systematic Review and Meta-Analysis of Interventions to Delabel Low-Risk Penicillin Allergies with Consideration for Sex and Gender

Overview

Aims: Sex and gender may influence penicillin allergy label (PAL) prevalence and outcomes. This review evaluates the effectiveness and safety of direct delabelling (DD) and oral challenge (OC) for low-risk patients and examines sex and gender differences in reporting and outcomes.

Methods: We searched PubMed, Database of Abstracts of Reviews and Effects, ClinicalTrials.gov, Cochrane Database of Systematic Reviews, International Pharmaceutical Abstracts, medRxiv, Ovid MEDLINE, and Ovid EMBASE until February 2024 for studies including DD or OC compared to no intervention, skin testing or other methods. Two reviewers assessed quality. Meta-analyses were conducted, and subgroup analyses were carried out if $I^2 >$ 75%. Descriptive data was analysed using NVivo 14 and reported narratively.

Results: From 1046 screened studies, 28 met inclusion criteria (two RCTs, 26 quasi-experimental studies). Sex at baseline was reported in 86% of studies, with 61% females: 18% disaggregated outcomes by sex with a female mean delabelling rate of 66%. Gender variables were not reported. OC was not found to be more or less as effective comparaed toskin testing in RCTs (risk ratio [RR] 1.04; 95% confidence interval [CI] 0.95, 1.13, $I^2 = 74\%$). DD interventions had a 27% delabelling rate (95% CI 10%, 50%, $I^2 = 96\%$), with nursing staff achieving 29% (95% CI 15%, 47%, $I^2 = 63\%$) and allergists/immunologists 6% (95% CI 0.00, 0.00, $I^2 = 20\%$). Quasi-experimental studies reported 90% delabelling for OC, with 59% by allergists/immunologists and 90% by pharmacists. Adverse events averaged 4% and were non-severe.

Conclusions: DD and OC are effective for delabelling low-risk penicillin allergies. Comprehensive data is lacking on sex and gender differences, indicating a need for further research.

Background

β-lactam antibiotics are often first-line agents for various infectious diseases from skin and soft tissue (5,87,88) to bloodstream infections (6,7). However, about 10% of the general population (7) and up to 15% of hospitalized patients carry a penicillin allergy label (PAL) (21). Penicillin allergy delabeling can be safely accomplished for 90% to 95% of individuals (89) through various means including penicillin skin testing (PST), oral challenge (OC), and direct delabel (DD) through questioning (7). PST has historically been the gold standard for assessment of PAL with a positive predictive value of between 50% to 75%, (7); however, interpretation depends on true prevalence of penicillin allergy in a population (62). Therefore, PST may be a poor screening tool in patients with low-risk penicillin allergies and OC is now recommended in low-risk populations (7,89,90).

Sex and gender variables are significant in understanding penicillin allergy (PAL) prevalence and outcomes. Historically, females report higher rates of adverse drug reactions (91) and penicillin allergies (22,23,73). However, it is not clear whether the association is with sex or gender or a combination thereof. There is speculation that the female propensity to drug allergy may be related to a multitude of factors including gender-related variables arising from social constructs such as differential use of healthcare and sex-related factors associated with genes, hormones as well as epigenetic factors that affect sex disparities associated with development and control of allergic conditions (78,81). Therefore, both biologic and gender-related factors may contribute to varied reporting of penicillin allergies and patient outcomes by sex.

The aim of this systematic review and meta-analysis was to identify, assess the quality of, and synthesize results from, studies reporting on the effectiveness and safety of penicillin allergy delabeling interventions in low-risk adult populations by DD or OC in comparison to no intervention, PST, or other interventions. Sex and Gender-Based Analysis Plus (SGBA+) information was extracted to understand sex and gender differences in penicillin allergy reporting and outcomes.

Methods and Design

The protocol and PRISMA-P 2015 checklist for this systematic review has been registered with PROSPERO (#336457). The protocol for this systematic review and meta-analysis can be found in Appendix A and the PRISMA-P 2015 checklist in Appendix B. The Cochrane Handbook for Systematic Reviews of Interventions (92) and the Centre for Review and Dissemination's Guidance for Undertaking Reviews in Health Care (93) were used as frameworks for conducting the systematic review. An integrated knowledge translation co-design strategy (94) with involvement of key stakeholders such as pharmacists,

physicians, nurses, a public citizens' council and administrative as well as leadership personnel was implemented to optimize protocol design.

Eligibility Criteria

Inclusion

- Studies involving patients with reported penicillin allergies
- Studies that include DD or OC
- Randomized controlled trials and non-randomized study designs
- Primary outcome must include penicillin allergy delabeling
- Adult (18 years of age or older) population

Exclusion

- Non-English language text (due to lack of funding for translator)
- Studies focusing solely on pediatric populations (<18 years of age) or where data cannot be separated for pediatrics and adults
- Animal and in-vitro studies
- Case reports, case series, editorials, opinions, and commentaries
- Delabeling of non-penicillin beta-lactams only
- Studies where all participants underwent PST as a first step

Literature Search

A systematic literature search was performed from inception to October 2023 and updated in February 2024 by a research librarian from the University of Waterloo. Databases searched included PubMed, Cochrane Database of Systematic Reviews, International Pharmaceutical Abstracts, Ovid MEDLINE, Ovid EMBASE, ClinicalTrials.gov, and medRxiv. The Search strategy for PubMed can be found in Appendix C. Title and abstract screening using Covidence (95) were conducted by 2 reviewers after calibration of the first 20 articles screened. The second screen of full-text articles was performed independently by 2 reviewers. Conflicts were resolved through discussion or an additional adjudicator.

Quality Assessment

The Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies (96) was used to assess study quality. Components included selection bias, study design, confounders, blinding, data collection methods, and withdrawals and dropouts. During the protocol design phase, our team selected the Cochrane's Risk of Bias assessment tool (97) to interpret risk of bias in randomized trials and the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) (98) tool for non-randomized trials and quasi-experimental studies. The change in tool was made given that 26 of 28 included studies were quasi-experimental and the EPHPP Quality Assessment tool is intended to evaluate a variety of intervention designs. Two reviewers independently completed the tool for each study, resolving discrepancies through discussion.

Interventions and Outcomes of Interest

The two delabeling interventions of interest were DD and OC. DD was defined as removal of an allergy after questioning or use of an algorithm only, and OC as the use of a penicillin, amoxicillin, or other penicillin-family antibiotic given orally to patients with a low-risk PAL. The primary outcome was the effectiveness of the intervention, measured as the proportion of persons with their penicillin allergy delabeled. The secondary outcomes included: 1) frequency of prescribed antibiotic therapies, 2) duration of antibiotic therapy, 3) secondary infections, 4) treatment success, reinfection, or re-admission, 5) cost of therapy or cost savings, and 6) prescribing practice changes over time. Comparison between intervention and control arms were made, where available.

Data Extraction

Microsoft Excel was used for data extraction and details are reported in the study protocol. SGBA+ information was extracted to understand differences in allergy reporting and outcomes associated with delabeling interventions. Variables from PROGRESS elements (place of residence, race/ethnicity/culture, language, occupation, gender/sex, religion, education, socioeconomic status, and social capital) were extracted to identify factors that may impact health equity from a gender lens (76). Initial calibration of data extraction was performed on 5 full-text articles considered for inclusion by 2 members of the research team and conflicts were resolved by discussion. Recording of individuals performing data extraction and the date

of data extraction was maintained in Covidence (95). Data available in manuscripts and supplementary material were considered.

Data Synthesis and Analysis

Studies were described based on patient characteristics. Definitions of low risk penicillin allergy were inductively and thematically analyzed (99) using NVivo 14 creating diagrams. Definitions provided in writing, algorithms, or acronyms (i.e., PEN-FAST) were analyzed by 1 reviewer and grouped by DD and OC. Other study level characteristics were narratively reported. For studies including OC, the denominator included all eligible for OC, and the numerator included those with successful OC. Secondary outcomes were categorized into 3-month intervals from 0 to 12 months post-intervention. For randomized controlled trials (RCTs), the intervention effect is expressed using relative risks and risk differences for categorical outcomes. Results of single-arm quasi-experimental studies are reported using proportions. The results from included studies were meta-analyzed using random-effects models. The Knapp-Hartang approach (100) was used to estimate between study heterogeneity for pair-wise comparisons. For quasi-experimental studies without a control arm, a random-effects proportional meta-analysis was conducted (101). Heterogeneity of results across studies was assessed using the Chi^2 statistic and quantified using the I^2 statistic. Pre-defined subgroup analyses potentially impacting delabeling intervention outcomes were conducted (102) to explore heterogeneity including patient sex (male, female), provider type (allergist/immunologist, pharmacist, nurse, primary care practitioner, other), and patient age (18 to <65 years versus >=65 years).

Results

Study and Population Characteristics

After screening 1046 citations, 28 studies were included of which 2 (7%) were RCTs (103,104), and the remaining 26 (93%) were quasi-experimental studies (49,89,105–128). The PRISMA flow diagram is shown in Appendix D. Both RCTs assessed OC vs. PST. Of the 26 quasi-experimental studies, 2 included only DD interventions, 16 included OC only, and 8 included both DD and OC. Descriptions of the study settings, population, sample size, inclusion criteria, and inclusion of DD and OC arms are found in Table 1.

Participant demographics including age and sex can be found in Appendix E. The mean age was reported in 24 studies (85%) with an average age of 56 years and range of 34 to 73 years (49,89,103–

106,109–117,119–127). Sex of participants at baseline was reported in 24 studies (86%), with a 61% female proportion in 22 studies (49,89,103–106,109–117,119,122–127); 2 studies included exclusively pregnant people (120,121). Five studies (18%) included both male and female participant demographic variables at baseline (49,89,111,119,123). Ten studies (36%) reported ethnicities of participants of which 88% were Caucasian, 2% Hispanic, 2% Black, 2% Pacific Islander, 1% Asian, 4% other ethnicity not defined, and <1% multiracial (49,104–106,108,116,117,119,126,127). In terms of quality assessment, 27 were considered weak (2 or more weak ratings) and 1 was moderate (one weak rating). Details of each component of the quality assessment are reported in Appendix F for each study.

Definitions of Low-Risk

Twenty studies (71%) included only low-risk participants (49,89,104,111–126,128). The remaining included a mix of low, moderate, and high-risk participants, of which the proportion of low risk varied between 44% to 50% in 5 studies (103,111,113,115,119), and 2% in one study (110). Definitions of low risk described in these studies are shown in Appendix G. Of the 11 studies that included DD, 9 themes emerged (Appendix H); gastrointestinal symptoms were noted in 7 definitions, tolerated since index reaction in 4, family history in 3, mild neurologic symptoms in 3, mild renal or hepatic impairment in 3, no recall of reaction in 2, pruritis in 1, thrush in 1, and unknown remote reaction more than 10 years ago in 1. For the 26 studies that included OC, 7 major themes were identified (Appendix I); non-severe cutaneous reactions were most frequent, appearing 34 times, unknown reaction in 18, side effects or intolerance in 12, absence of anaphylaxis or angioedema in 9, no personal reaction experienced in 8, non-life-threatening reaction in 7, and tolerated since index reaction was noted in 3 definitions.

Effectiveness of Interventions

OC was not found to be more or less effective compared with PST followed by OC in the RCTs (2 studies, RR 1.04; (95% CI 0.95, 1.13), I^2=74%) (Figure 1). The pooled risk difference was 0.03 (95% CI -0.05, 0.12). A total of 1,499 participants were included in studies evaluating DD with 27% (95%CI 10%, 50%) of participants having the allergy label removed; however, there was a high degree of between-study heterogeneity (I^2= 96%) (Figure 2a). Subgroup analysis by age, clinical setting, and health care provider group are shown in Figure 2b-d. There were significant subgroup differences by setting and across health care providers, although substantive heterogeneity remained for most groups. OC was described in 24 quasi-experimental studies (2,752 participants) with 90% (95%CI 83%, 95%) of participants having the allergy

label removed; however, there was a high degree of heterogeneity (I^2= 93%) (Figure 3a). Figure 3b-d show subgroup analyses for the OC studies by age, clinical setting, and health care provider group with Figures 3c and 3d showing significant subgroup differences.

Sex-Disaggregated Outcomes

Sex disaggregated outcomes were reported in 5 studies (49,89,108,123,126). Mak and Zhang focused on pregnant populations (120,121). Chua's study assessed both DD and OC; however, not all study participants were categorized as low risk (111). The remaining 4 studies only assessed OC (49,89,123,126). A random effects meta-analysis by sex was conducted showing the proportion delabeled as 73% among females (22%; 100%), I^2=99%, and 77% among males (48%; 94%), I^2=99% (Figure 4). No significant sex differences were found (p = 0.87 for subgroup differences). Given the high degree of heterogeneity, further subgroup meta-analyses were not performed. Chua (111) and Trubiano (119) studied populations with a mean age 65 years or greater and allergy assessments were conducted by nursing staff in a hospital setting. The meta-analysis of these 2 studies showed 28% of females (16%; 45%), I^2=4% and 36% of males (5%; 87%), I^2=89% were delabeled indicating higher heterogeneity in the meta-analyses of male participants but a greater proportion of males delabeled. In the studies by Iammatteo (49), Stevenson (89), and Fransson (123) the mean age of the populations studied was 65 years in ambulatory settings without exact health care provider involved in intervention defined; 95% of females (59%; 100%) I^2=79% and 95% of males (80%; 99%) I^2=0% were delabeled, with higher heterogeneity in females but similar delabeling rates overall. In Copaescu's RCT, 2 female participants, one in DD and another in the OC arm, experienced positive immune mediated OC within 1-hour post-intervention (104); however, the outcomes were not distinctly sex-disaggregated and therefore were not included in the meta-analysis.

PROGRESS Factors

PROGRESS factors such as sex, age, and ethnicity are described under "Participant Demographics", with race and ethnicity often used interchangeably and without definitions for each variable. None of the studies described lived gender of the participants, culture, language, occupation, religion, education, socioeconomic status, or social capital. The country of study conduct was the major descriptor for place of residence, with 11 studies carried out in the United States (49,103,106,108,110,116,117,122,124,126,128), 5 in Australia (89,109,111,115,119), 3 in Canada (112,120,121), 2 in the United Kingdom (107,118), 2 in New Zealand (105,113), 2 in Norway (125,127), 1 in Scotland (114), and 1 in Denmark . None of the studies

were conducted in low-to-middle-income countries.

Secondary Outcomes

Due to the variance in reporting secondary outcomes, no meta-analyses were conducted. Chua's study examined antibiotic prescribing appropriateness, mortality rates, re-admissions, IV antibiotic duration, and total antibiotics prescribed (111). Appropriateness increased from 67% pre-intervention to 78% post-intervention, in-hospital mortality was 2% for both delabeled and non-delabeled groups, with higher post-discharge mortality in non-delabeled (5% vs. 4%), re-admissions at 90 days were higher in non-delabeled (31% vs. 29%), median IV antibiotic duration was 3 days for both groups, and total antibiotic use was 37% in non-delabeled and 40% in delabeled groups (111). Length of stay was reported in 2 studies (105,111); length of stay showed no significant difference in Chua's study, while Du Plessis reported six days for inaccurately labeled patients versus nine days for those with confirmed allergies. Two studies (38, 47) reported the proportion of participants prescribed any penicillin before and after delabeling with the proportion receiving penicillin being significantly higher in the delabeled groups (111,119). Chua reported cephalosporin use was 29% in non-delabeled and 10% in delabeled groups; carbapenem use was 1% in both, vancomycin use was 3% vs 2%, clindamycin 3% vs 1%, and fluoroquinolones 5% vs 3% (111). Ham provided pre- versus post-study numbers expressed as counts: cephalosporins 21 vs 7, carbapenems 1 in both arms, vancomycin 9 vs 2, clindamycin 5 vs 3, and fluoroquinolones 10 vs 0 (110). Continuity of delabeling was described across 5 studies; Iammatteo reported 4 participants with mild delayed cutaneous symptoms and 1 with oropharyngeal symptoms (49), Ramsey describes a delayed rash on day 17 of amoxicillin-clavulanate use, and a case of facial swelling, nausea, and vomiting the day after OC (106), Devchand described a case of delayed rash post-discharge (109), Chua describes 2 re-labeled cases at 90-day follow-up without further details (111) and Du Plessis observed 3 patients with delayed hypersensitivity reactions following repeat penicillin administration (105).

Safety of Oral Challenge

The number and nature of reactions in the 26 studies involving OC, including 2 RCTs and 24 quasi-experimental studies can be found in Appendix J. There was an average of 4% of participants who experienced non-severe reactions. None reported severe reactions such as severe cutaneous delayed reactions, hepatic or renal impairment, neurological deficits, or anaphylaxis.

Discussion

This systematic review and meta-analysis evaluated the efficacy and safety of DD and OC in low-risk patients with PAL, while also exploring sex and gender-related factors. Only two RCTs compared OC vs PST with no comparative studies between OC and DD or between DD and PST identified. On average, about 25% of low-risk patients were delabeled using DD and 90% using OC. The literature lacks consistency in reporting penicillin allergy testing outcomes by sex, and there is no unified definition of "low risk." No studies using DD approaches reported delabeling rates by sex. In the 26 studies involving OC, adverse reactions were rare (less than 5%), with no severe reactions or anaphylaxis were reported. These findings underscore the safety and efficacy of both OC and DD for delabeling low-risk penicillin allergies, highlighting their potential to enhance antimicrobial prescribing practices.

Previous reviews on penicillin allergy delabeling have not focused specifically on low-risk populations or provided comparisons of controlled studies. A 2024 review of outpatient OC by non-allergists, including 12 studies, reported no serious adverse events but noted low to moderate quality studies (129). This is consistent with our findings where most participants tolerated intervention with few experiencing adverse reactions; however, when quality assessment was performed, 27 of 28 studies were of low quality with only one assessed as moderate, indicating a need for higher quality studies. Another systematic review aimed to assess the role of routine penicillin allergy testing and safety of delabeling approaches found 5 studies that addressed safety of OC in comparison to PST; however, authors pooled randomized and non-randomized studies in the reported meta-analysis whereby we elected to separate results from RCTs and quasi-experimental studies (130). Our findings from 2 RCTs by Mustafa and Copaescu (103,104) support that OC was an effective and safe alternative to PST followed by OC for delabeling of low-risk penicillin allergies. Despite supporting the effectiveness and safety of delabeling interventions, the heterogeneity of the quasi-experimental studies limited the strength of meta-analyses.

In our knowledge synthesis, OC interventions were examined across 16 studies and were shown to successfully remove the penicillin allergy label in an average of 90% of participants, as indicated by our proportion meta-analysis (Figure 3), though with substantial heterogeneity between studies. In contrast, DD interventions were explored in 8 studies; however, none of these studies reported on adverse events, as no actual allergy challenges were performed. Consequently, DD interventions should be approached cautiously, limited to cases where careful assessment can ensure that allergy label removal is safe. Thematic analysis of studies describing DD interventions suggests that successful delabeling was often associated with factors

such as mild side effects (e.g., gastrointestinal symptoms or thrush), remote or unknown reactions, lack of reaction recall, or family history of allergy without a personal history.

This review is the first to address sex, gender, and equity-related factors in penicillin allergy delabeling. Studies by Chua (111) and Trubiano (119) involving older participants, and hospital settings showed lower proportions of females delabeled compared to males. In contrast, studies by Iammatteo (49), Stevenson (89), and Fransson (123) involving younger participants and ambulatory settings, showed similar delabeling proportions between sexes. These differences might reflect age-related or setting-specific factors influencing delabeling outcomes. Although RCT outcomes were not sex-disaggregated, Copaescu's study reported positive immune-mediated reactions in one female participant in both the OC and PST arms (31). This variation by age, setting, and clinician involvement could indicate the need for further exploration of sex-related factors in prospective trials. The review also noted the scarcity of studies focusing on pregnant populations, with only two quasi-experimental studies including obstetrical patients (120,121). None of the studies considered lived gender, cultural factors, or other social determinants. Research was conducted in high-income countries, with limited representation from low-to-middle-income countries and long-term care settings. The lack of gender-related outcome reporting underscores the importance of understanding the impact of these variables on clinical outcomes of health research. Bauer's paper introduces implementation science for non-specialists (131), while Tannenbaum discusses integrating sex and gender in research (84), both highlighting important strategies for addressing factors related to health inequities.

Some limitations of this review are that only studies available in the English language were included and heterogeneity of results for quasi-experimental studies limits the ability to make clear recommendations on the magnitude of effect of delabeling by DD or OC in non-RCTs. Limitations within the literature include a paucity of sex-disaggregated outcomes for both safety and efficacy of delivered interventions and limited information related to health equity factors.

Conclusion

Low risk penicillin allergies can safely and effectively be assessed for delabeling either by DD or OC. Data related to sex are limited and data for gender are lacking, therefore presenting an opportunity for future research.

Chapter 3 : Unpacking Oral Challenge Protocols: Reactions, Predictors, and Practices for Delabeling Low-Risk Penicillin Allergies

Overview

Background: Oral challenges with amoxicillin or other penicillins are safe and effective for delabeling low-risk penicillin allergy histories. While approximately 90% of reported penicillin allergies can be safely delabeled, detailed data on reaction frequency, types, and timing during and after delabeling interventions remain limited. Such data are crucial to optimizing protocols and integrating oral challenges into routine practice. This study aims to characterize the interventions commonly used for oral challenge, classify reported reactions, and identify reported predictors of hypersensitivity reactions in randomized controlled trials and quasi-experimental studies involving an oral challenge for patients with low-risk penicillin allergies.

Methods: This study leverages data from a systematic review and meta-analysis assessing the effectiveness of oral challenge interventions in patients with low-risk penicillin allergies. This descriptive analysis summarizes the adverse reactions experienced among patients in published studies who received oral challenge. Participant demographics, intervention protocols, frequency, type, and timing of post-challenge adverse reactions are reported. Reactions are categorized as immediate, delayed, or other, with frequencies summarized using descriptive statistics. A random effects meta-analysis quantifies a pooled adverse reaction rate. Predictors of hypersensitivity reactions were synthesized narratively.

Results: Across 26 studies (2 randomized trials, 24 quasi-experimental studies) evaluating an oral challenge for patients with a low-risk penicillin allergy, the average participant age was 56 years, with a predominance of females (61%) and limited ethnic diversity with 88% reported or identifying as White. Amoxicillin was the most frequenty used oral challenge agent, typically administered as a single 250 mg oral dose. The incidence of reaction or non-delabeling was 4% (95% Confidence Interval 3%, 6%), $I^2 = 43\%$, $P = .0001$. Cutaneous manifestations, such as rashes, were the most frequent reactions. Delayed reactions, primarily mild maculopapular rashes, were uncommon and managed with antihistamines or topical steroids. Risk factors for oral challenge reactions included higher baseline allergy burden and shorter intervals to oral challenge since the index reaction.

Conclusion: Oral challenge strategies to delabel low-risk penicillin allergies can involve single doses of amoxicillin or other penicillins with monitoring protocols that can be managed in ambulatory settings. However, although these delabeling strategies are becoming more prevalent, continued study of standardized protocols and follow-up are essential for effective and replicable delabeling strategies. Future research should prioritize diverse populations and equity-driven frameworks to improve generalizability to all individuals and to resource limited settings.

Background

Oral challenge is widely recognized as a safe and effective method for assessing penicillin allergies in low-risk population (20,132,133). However, a critical gap remains in understanding the timelines to and types of reactions that may occur during or after oral challenge interventions. This knowledge is essential not only for optimizing the safety and efficacy of oral challenge protocols but also for facilitating their integration into routine clinical practice (134). By improving understanding of the characteristics, timelines, and predictors of hypersensitivity reactions, this work seeks to empower healthcare providers to confidently delabel patients with inappropriate penicillin allergy labels. In doing so, it will help reduce the unnecessary avoidance of first-line antibiotics, enhance antimicrobial stewardship, and improve patient outcomes across diverse healthcare settings (7,12,135). Specifically, this study aims to comprehensively describe the characteristics of oral challenge interventions, categorize the observed and reported reactions following oral challenge, and identify predictors of hypersensitivity reactions in studies designed to delabel low-risk penicillin allergies.

Methods

This study leverages data from a previously published systematic review and meta-analysis focused on penicillin allergy delabeling in low-risk populations (133). Details of the methods are available in both the published study protocol (136) registered in PROSPERO: CRD42022336457 and in a manuscript reporting the primary findings (133). Briefly, a comprehensive search strategy was conducted across multiple databases (PubMed, Cochrane Database of Systematic Reviews, International Pharmaceutical Abstracts, Ovid MEDLINE, Ovid EMBASE, ClinicalTrials.gov and medRxiv) between their inception and February 2024. Two independent reviewers initially screened titles and abstracts prior to that of relevant full-text articles. This descriptive analysis uses data from all identified randomized trials and quasi-

experimental studies evaluating individuals classified as having a low-risk penicillin allergy history who underwent oral challenge interventions, as these participants were directly evaluated for tolerability based on post-challenge outcomes. Low-risk was defined in the initial systematic review using thematic analysis of all eligibility criteria for inclusion in oral challenge arms across the 26 studies in which seven major themes were identified: non-severe cutaneous reactions, unknown reaction, side effects or intolerance, absence of anaphylaxis or angioedema, no personal reaction experienced, non-life-threatening reaction, and tolerated since index reaction (133). Patients included in direct delabeling interventions without oral challenge were excluded from this analysis.

Baseline demographic and clinical characteristics, intervention protocols, and reported index reactions to penicillins (reason for penicillin allergy label) were extracted as described by the authors and reported by participants. The primary outcomes of interest for this study are the characteristics of reported reactions after oral challenge intervention, including the time to onset, classification of reported reactions, and potential predictors of hypersensitivity reactions. Any reaction to oral challenge or reported reason that led to lack of removal of the allergy label based on the discretion of the study authors were described as non-delabeled. The mean incidence of reactions (or non-delabeling) occurring after oral challenge administration was described in the original systematic review and meta-analysis but is also briefly reported herein. Given that none of the reactions were severe in nature, reactions were categorized into the following groups: 1) non-severe immediate reactions (within 1 hour of oral challenge), 2) delayed non-severe reactions (occurring more than 1 hour after oral challenge), and 3) other reported reactions.

Descriptive statistics, including means and ranges, were used to summarize patient demographics, intervention characteristics, and baseline reaction histories. A random-effects proportional meta-analysis was conducted (4), heterogeneity of results across studies was assessed using the Chi^2 statistic and quantified using the I^2 statistic, and the DerSimonian-Laird approach was used to estimate between study heterogeneity. All oral challenge arms across all intervention types were pooled together for the purpose of this meta-analysis. Factors associated with an increased risk of post-oral challenge reactions, as reported by study authors, were synthesized and described narratively.

Results

Population Characteristics

As described in the initial systematic review and meta-analysis, there were 26 studies (2 RCTs, and 24 quasi-experimental studies) identified that included an oral penicillin challenge among low-risk patients. The mean age was reported in 24 studies (85%) with an average age of 56 years, ranging from 34 to 73 years (49,89,103–106,109–117,119–127). Most study participants were female (61%) (49,89,103–106,109–117,119,122–127) with two studies including exclusively pregnant people (120,121). Five studies included both male and female participant demographic variables at baseline (49,89,111,119,123). Ten studies reported ethnicities of participants of which 88% were White (49,104–106,111,116,117,119,126,127).

Index Reactions Leading to Allergy Labeling

The self-reported index reactions were described in 18 (69%) of the studies (49,103,105,106,110–115,117,120–122,124–126,128); details regarding all reported index reactions can be found in Table 2. Although index reactions were reported, these included both low-risk and high-risk individuals without further stratification by allergy risk or correlation with tolerability of the oral challenge. Based on the reported data, diffuse rash occurring more than 10 years prior (or timeline not described) was reported in 40% of participants across 8 studies (49,103,106,111,114,115,120,121) followed by childhood exanthem in 35% (min 9%, max 76%) across 5 studies (105,111,113,115,128) and urticaria in 29% across 9 studies (min 9%, max 42%) (49,103,106,110,111,120–122,124,125).

Oral Challenge Intervention Characteristics

In the 26 studies for which oral challenge in the setting of a low-risk penicillin allergy was performed, amoxicillin 250 mg as a single oral dose was an option in 42% of studies (110,111,113,115–117,119,122,125,126,128) (Table 3). Amoxicillin 500 mg administered orally was described in 27% of studies (106,111,114,121,123,124,127); however, frequency of dosing varied from once daily to twice daily administration for multiple days. Graded oral challenge strategies were described in 19% of studies (103–105,112,118). In the study by Alnaes et al., the penicillin for which the index reaction occurred was used if known, otherwise amoxicillin was selected (127). Other penicillins for oral challenge were considered in fewer studies as can be seen in Table 3. With respect to provider monitoring, nurses were involved in 27% (106,109,111,113,115,118,119), pharmacists in 15% (105,110,117,126), allergists or immunologists in 12%

(103,120,124), primary care providers in 4% (112), and other or non-defined providers in 38% (49,89,104,114,116,121,122,125,127,128). One study by Fransson et al. included patient self-completion (123).

Incidence of Reaction to Oral Challenge

Of 26 studies in which participants received an oral challenge, the pooled weighted mean incidence of reaction or non-delabeling due to an experienced reaction, or non-delabeling at discretion of the study authors was 4% (95% Confidence Interval 3%, 6%), I^2=43.2%, P=0.0001 (Figure 5). None of the reported reactions were severe in nature. The reaction rate varied across studies with 6 studies describing all participants as tolerating oral challenge. In 13 studies, between 1% to 5% of participants were not delabeled; in 5 studies 6% to 10% of participants were not delabeled. Reactions to oral challenge occurring at a rate greater than 10% were described in studies by Kuruvilla et al. (124) and Iammatteo et al. (49); details regarding the reported reactions can be found in Table 3.

Immediate Reactions

In 2 RCTs, reactions to oral challenges were infrequent and non-severe. Copeascu et al. reported immune-mediated reactions in 0.5% of participants (one per study arm) (104) while Mustafa et al. reported three mild cutaneous reactions, all resolving with oral antihistamines (103). Of 24 quasi-experimental studies, including two involving pregnant individuals, 13 reported no reactions, mild non-allergic symptoms, or non-severe cutaneous reactions, with seven studies (27%) reporting no reactions during oral challenge (109,115–117,120,123,126). Mak et al., in a study of pregnant individuals, reported 4 delayed maculopapular rashes treated with topical steroids and oral antihistamines and 1 case of vomiting attributed to pregnancy (121). Ham et al. found 98% of participants were delabeled, with two retaining their allergy label due to mild, non-IgE-mediated symptoms (lip tingling and gastrointestinal discomfort) (110). Kuruvilla et al. observed 3 non-IgE-mediated reactions (pruritus, chest tightness, dizziness); all self-resolved without treatment (124). Rozario et al. reported that while 98% of participants were eligible for delabeling, only 64 of 79 who tolerated oral challenges opted to remove the allergy label from their electronic medical record (122).

Delayed Reactions

In 6 quasi-experimental studies, non-severe delayed reactions were reported. Chua et al. report that 97% of participants completed the oral challenge successfully, with 6 documented reactions: 3 non-immune-mediated (fever with baseline urosepsis, vomiting, and pruritus without rash) and 3 delayed immune-mediated reactions suspected to be T-cell-mediated, occurring 5–7 days after oral challenge intervention (111). Du Plessis et al. reported no immediate reactions, but 3 cutaneous reactions occurred within 72 hours (105). Ramsey et al. found 97.9% of participants tolerated the intervention with 1 delayed rash after 17 days and 1 case of facial swelling, nausea, and vomiting the day after challenge with amoxicillin-clavulanate, managed successfully with antihistamines (106). Trubiano et al. reported a 95.8% delabeling rate, with 10 presumed immune-mediated reactions (9 delayed rashes, 1 immediate rash, and others including throat tightness and fever), with none requiring epinephrine (119). Fransson et al. observed 19 of 20 reactions involved skin symptoms, with 13 occurring 3 days post-challenge (123). In the only study with 6-month follow-up (Livirya et al.), 10% of participants had allergy labels re-applied without detailed explanations (113).

Other Reported Reactions

Unique patient factors contributed to reactions in 2 studies, and 1 study described broad treatment for notable reactions. In the Steenvorden et al. study, a patient with bronchial obstruction experienced worsening respiratory symptoms, which resolved with ipratropium-salbutamol inhalation; this was deemed unlikely to be IgE-mediated, although the patient was not delabeled (125). In the study by Savic et al. one patient developed hand urticaria after the second dose of amoxicillin. Further questioning revealed a history of widespread urticaria, which the patient did not disclose, as they were eager to participate in testing. Tucker et al. studied marine recruits, of whom five (2%) experienced reactions: two with rashes, two with unknown reactions, and one case of hives; in these instances, epinephrine was administered empirically to prevent escalation although anaphylaxis was not reported (128).

Risk Factors that Correlated with Reaction to Oral Challenge

Two studies explored risk factors linked to positive oral challenges and defined populations deemed “low risk”. Iammatteo et al. found a correlation between the number of baseline reported allergies or intolerances and oral challenge outcomes (49). Patients with allergic reactions had a median of 3 baseline allergies or intolerances (IQR 2.5–3.5), compared to 2 (IQR 1–4) in those with non-allergic reactions and 1

(IQR 1–2.5) in those with no reaction (P = 0.02) (49). Stevenson et al. evaluated 8 definitions of low risk, including timing and severity of index reactions (89). The optimal model, suited for outpatient settings, identified low-risk reactions as those occurring over 1 year prior with mild symptoms (e.g., benign rash without mucosal involvement). Among these low-risk patients, 97.1% tolerated oral challenge without any cases of anaphylaxis.

Discussion

This study examines the characteristics of participants undergoing oral challenge to delabel low-risk penicillin allergies, the interventions used, and post-exposure adverse reactions. The findings support oral challenge as an effective, safe, and practical strategy, with low adverse reaction rates and high success in delabeling. In this adult population, the mean age was 56 years with a notable female predominance (61%), reflecting the higher reported prevalence of penicillin allergies in women. Ethnicity data were inconsistently reported, with most participants identifying as White and all studies were conducted in higher income countries. This underscores the need to fully ascertain participant ethnicity and include more diverse populations in future studies to ensure equitable access to care and improve the generalizability of rash assessments during penicillin oral challenge interventions across all skin tones, particularly as cutaneous reactions are the most reported reaction to oral challenge. Furthermore, availability of resources to conduct oral challenge interventions in low and middle-income countries requires further study to determine the best strategies to implement these interventions in resources limited settings.

Amoxicillin was the preferred agent for oral challenge, likely due to its accessibility, tolerability, and safety profile. Most studies used single-dose or short-duration challenges at doses of 250 mg or 500 mg, with less frequent use of graded challenges or other penicillins. Variability in dosing and provider roles suggests the need for standardized protocols. Nurses and pharmacists were commonly involved in monitoring, demonstrating the feasibility of non-physician healthcare professionals in scaling delabeling interventions.

No clear link emerged between the agent or dose used in oral challenges and the risk of reactions. However, based on tolerability information on follow-up with patients who were prescribed penicillins after oral challenge, there may be a correlation between the use of amoxicillin-clavulanate and intolerance or mild hypersensitivity reactions (106). This is supported by a study that used spontaneous reporting of adverse drug reactions in Italy by Salvo et al., which found higher rates of gastrointestinal (13% vs. 7%), hepatic (4% vs. 1%), and hematologic (2% vs. 1%) reactions with amoxicillin-clavulanate compared to amoxicillin,

despite skin reactions being more common with amoxicillin (82% vs. 76%) (137). Furthermore, other studies show a correlation between oral challenge with amoxicillin/clavulanate and the development of hepatotoxicity and pancreatitis (138,139). Therefore, amoxicillin-clavulanate is a β-lactam characterized by a unique association with hepatopancreatic adverse drug reactions.

The absence of severe reactions supports oral challenge as a first-line strategy, even in vulnerable populations such as pregnant individuals who are assessed as having a low-risk penicillin allergy. This was supported by a cohort study conducted by Wong et al., which evaluated penicillin oral challenges during the antepartum and postpartum phases and found the approach to be safe and effective in the antepartum phase (140). The authors also noted that deferring oral challenges to the postpartum period poses a significant barrier to penicillin allergy delabeling (140). However, even though oral challenge was relatively well-tolerated across the studies included in this analysis, follow-up is important as mild delayed reactions such as maculopapular rashes were reported. Studies with extended follow-up indicated some relabeling, emphasizing the importance of patient education and robust follow-up to sustain benefits and understand long-term sequalae associated with delabeling interventions. One study suggested a correlation between the number of reported allergies and reaction likelihood, indicating potential for risk stratification (49). Timing since the index reaction and a benign nature of the reaction were also important factors, supporting their inclusion in future risk assessment tools (89).

This research has some limitations. Inconsistent reporting of demographics, comorbidities, and equity factors, along with heterogeneous challenge protocols, complicates cross-study comparisons. Many studies lacked standardized definitions for allergic versus non-allergic reactions, and long-term outcomes were often underreported. The inclusion of participants with low and high-risk baseline reactions without linkage to eligibility for oral challenge leads to the inability to clearly interpret how reported baseline reactions correlate with outcomes. Also, the underrepresentation of vulnerable and diverse populations limits generalizability. Most studies relied on short-term follow-up and patient-reported data, which are prone to recall bias. Further, the research was largely conducted in high-income countries with few randomized controlled trials, highlighting the need for more rigorous, standardized, and equity-informed studies in this field.

Conclusion

This descriptive analysis underscores the critical role of oral challenge interventions in improving antibiotic stewardship by safely delabeling low-risk penicillin allergies. Most oral challenge interventions

involve a single 250 mg dose of amoxicillin, with most participants tolerating the challenge. Reactions were mild and primarily cutaneous in nature, with few delayed reactions having occurred. Implementing standardized, evidence-based protocols in diverse healthcare settings, including primary care and community pharmacies, is feasible and has the potential to enhance accessibility to penicillin allergy assessment interventions.

Chapter 4 : A Cross-Sectional Study to Measure the Association Between Sex and the Presence of a Penicillin Allergy Label Upon Hospital Encounter

Overview

Background: Penicillin allergy labels (PALs) affect about 10% of people, are mostly low-risk, and more common in females. Sex-based differences in prevalence and characteristics remain unclear. This study examined associations between sex, PAL and relevant covariates, in an Ontario ambulatory hospital population.

Methods: A cross-sectional study of adults (≥18 years) seen at the hospital's Urgent Medicine Clinic from 2015–2024 was conducted. Descriptive statistics compared patients by PAL status. Unadjusted and multivariable logistic regression models evaluated associations between sex and PAL, adjusting for covariates. Analyses used R-Studio.

Results: Among 29,645 patients (59.7% female), 3,026 (10.2%) had a documented beta-lactam allergy, of which 2,777 (9.4%) were PALs, and most (91.7%) were low risk. Females were twice as likely to have a PAL (11.6% vs 6.0%; unadjusted OR 2.17, 95% CI 2.14–2.19) and more often reported multiple medication allergies (30% vs 16%; OR 2.25, $p < 0.05$). In a multivariable model adjusting for covariates, female sex (OR 1.47, 95% CI 1.34–1.62), atopic conditions (OR 1.46, 95% CI 1.29–1.66), older age (>80 years: OR 1.16, 95% CI 1.02–1.32), and number of other medication allergies (2: OR 10.44, 95% CI 9.28–11.74; ≥3: OR 13.33, 95% CI 11.72–15.16) were associated with higher odds of PAL.

Conclusion: About 10% of patients had a PAL, mostly low-risk and with female prevalence. Multivariable analysis identified female sex, atopic conditions, older age, and multiple medication allergies as independent predictors, whereas autoimmune and metabolic conditions were not. Longitudinal studies incorporating validated allergy data and intersectionality can further guide equitable allergy evaluation.

Background

β-lactam antibiotics are first-line in the treatment of many infections (6,141,142). However, 5 to 15% of patients are labelled as penicillin allergic (7,26,36,133), which may lead to use of second-line agents, suboptimal prescribing, and adverse outcomes. The latter may include longer hospital stays, higher costs, and increased toxicity associated with use of second-line agents in individuals with a penicillin allergy label (PAL) compared to those without (142). Across various studies, approximately 95% of individuals with a PAL can tolerate penicillins through delabeling interventions (7,89,111,143). A recent systematic review and meta-analysis estimated that 30% of patients with low-risk penicillin allergies could undergo direct delabeling through structured questionnaire or decision tree algorithm use, and over 90% could be delabeled using an oral challenge (133). However, few epidemiological studies have explored potential sex differences in the prevalence or predictors of a PAL (22,23,73). This is vital to determine whether sex is a factor that should be considered when determining the probability of accuracy of a PAL in risk scoring systems and in assessment of people with PALs in clinical settings.

Evidence from a small number of studies suggests sex-based variation in PALs, although the findings are inconsistent. Park et al. found that female sex was associated with higher odds of a positive penicillin skin test (PST) among adults attending a pre-operative clinic (OR 3.6, 95% CI 1.9–7.2), though key confounders such as comorbidities were not controlled for (22). Similarly, Voelker et al. reported that adult females were 10 times more likely to have a positive PST result in an inpatient setting (23). In contrast, Fox and Park found no significant sex difference in the prevalence of PST among children with a PAL ($p=0.5198$), suggesting the need for further exploration between factors impacting the difference between adult and pediatric age groups (73). Given the inconsistent results and limited strength of evidence on the correlation between sex and PAL (22,73), it remains unclear if true differences that are generalizable exist or if confounding factors account for differences in PAL among females and males. Determining whether other factors can better explain the perceived sex difference in PAL presence could help refine measurement and scoring tools for assessing PALs.

Other risk factors which may be correlated with increased presence of PAL in the general population include multiple allergies on a patient's profile (67), older age at presentation of allergic reaction (67), type of beta-lactam administered (67), atopic conditions, obesity (69) and potential genetic polymorphisms for cytokines involved in the regulation of immediate hypersensitivity reactions (67). A challenge in existing literature is inclusion of various confounders and consideration of gender or intersectional factors that may

be associated with a PAL. Social and demographic factors, such as age, sex, and race, may also influence the presence, reporting, or classification of PALs. Moreover, intersectionality variables may improve the capture of social and structural factors that influence healthcare access, diagnostic labeling such as PALs, and patient–provider communication. Accounting for PROGRESS factors (Place of residence, Race/ethnicity, Occupation, Gender, Religion, Education, Socioeconomic status, and Social capital) may guide clinicians in determining whether there are any disparities in who receives a PAL and reveals whether certain groups are more likely to be mislabeled, thereby providing opportunities to address equity and accuracy of allergy documentation and subsequent antibiotic use.

The objective of this study is to assess if an independent association exists between sex assigned at birth and presence of a PAL after controlling for potential confounders. Sex differences in the association between other correlates (atopic conditions, autoimmune disorders, obesity, total number of drug allergies) with PAL are assessed along descriptive analyses related to gender and equity (16), where available.

Methods

Study Design and Source Population

This cross-sectional study utilizes de-identified electronic medical record (EMR) data (2015-2024) from adults (≥18 years) with an encounter in an Urgent Medicine Clinic at an Ambulatory Care Hospital located in a large urban centre in Ontario, Canada. Exclusion criteria were non-urgent encounters, and patients with missing sex data in the electronic medical record (EMR). Non-Urgent Medicine Clinic encounters (procedure room and surgical encounters) include cases that are not intended for the short-stay medical unit which provides urgent assessment, investigation and management of medical conditions. In patients with more than one encounter over the study period, only the first encounter was included. This study received ethics approval from Women's College Hospital (REB #2024-0055) and the University of Waterloo's Clinical Research Ethics Board (45818). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cross-sectional studies was applied to this manuscript (144).

Exposure and Outcome Variables

The main exposure variable of interest, sex assigned at birth, was defined based on the recorded sex in the EMR: male or female. Due to small sample sizes, non-binary, X, other, or unknown levels of this variable were not included in this analysis.

The primary outcome, PAL presence, was defined as a listed allergy to penicillin in the EMR. All allergy labels were standardized if entered as free text for penicillins (aminopenicillins, antipseudomonal penicillins, antistaphylococcal penicillins, and natural penicillins) and non-penicillin beta-lactams (cephalosporins, carbapenems, and monobactam) (Appendices K and L).

Secondary outcomes were investigated in those with a PAL and included high-severity PAL and the presence of one or more non-PAL medication-related allergy (medications with a drug identification number by Health Canada, excluding natural health products and supplements). PAL severity was defined as low risk (severity not reported or low risk selected) and high risk (moderate or high risk selected), based on documented clinical details at the patient's encounter. PAL severity is found as a drop-down menu in the EMR; however, definitions are not provided to ensure consistent reporting across clinicians entering the allergy label severity.

Comorbidities and Other Risk Factors

Co-morbidities and other risk factors correlated with PAL based on existing literature (presence of multiple medication class allergies, atopic conditions, obesity, and immune-mediated inflammatory conditions), class of beta-lactam administered (penicillins, cephalosporins, carbapenems, and monobactam), were assessed in this study as additional exposures of interest and potential confounders for the association between sex and PAL. The disease co-factors are defined based on the medical problem list on admission in the electronic medical record (EMR) as ICD-10-CA codes (see Appendix M), and obesity is defined in keeping with the World Health Organization definition of a BMI over 30 either calculated using height and weight (145), or if present as a field in the EMR under a diagnosic ICD-10 code.

Statistical Analysis

Descriptive statistics were reported to characterize the study population. Counts, percentages, and frequencies were used to describe categorical variables, and continuous variables were reported as means

with standard deviations or medians with interquartile range. PROGRESS factors were narratively summarized, where available.

Logistic regression models estimate unadjusted odds ratios and 95% confidence intervals for the association between sex and presence of PAL (primary outcome), and between sex and secondary outcome (severity of PAL and presence of another non-PAL medication-related allergy). Similarly, the association between the presence of comorbidities (atopic, autoimmune inflammatory, and obesity) and PAL were tested using logistic regression. For the metabolic condition variable of obesity, height and weight were available together in the dataset for 2% of the population making BMI calculation not feasible; therefore, the ICD-10 codes associated with obesity were used due to missingness. Comorbidity-related associations with PAL were also stratified by sex and reported in a Forest Plot.

Adjusted odds ratios and 95% confidence intervals were estimated for the association between sex and PAL using a multivariable logistic regression model with the following covariates: age, number of drug allergy labels, and comorbidities. Specifically, age at first encounter was operationalized as a categorical variable of less than 65 years, 65 to 80 years, and greater than 80 years. This approach was taken as PALs may be more correlated with older age (146) and antibiotic utilization often increases with age (147). The number of drug allergy labels was defined using a categorical variable (0-1, 2, or 3+), and the presence of comorbidities in each of the atopic conditions, autoimmune inflammatory conditions, and metabolic conditions, were coded as binary variables (0=not present, 1=present).

Firth's Bias-Reduced Logistic Regression R Package was applied when a logistic regression model failed to converge due to small cell sizes. Data cells with fewer than 6 observations have been suppressed in accordance with the institutional Ethics agreement. All analyses based on small numbers should be interpreted with caution. Model assumptions and diagnostics were checked using standard methods. R Version 4.3.3, R-Studio was used to conduct all analyses (148).

Results

Population Characteristics and Allergy Label Prevalence

There were 29,645 patients seen at the Urgent Medicine Clinic, including 17,707 females (59.7%). The mean age for patients was 54.7 years (SD=19.8) with mean age by sex being 53.9 (SD=20.1) years for females and 55.8 (SD =19.3) years for males (Table 4). Of the entire cohort, 8.5% had an atopic condition,

5.2% with an autoimmune condition, and 1.6% were living with obesity. Across the entire cohort, 24.4% had a documented medication related allergy, including PAL (30.1% females, 16% males).

Of those with any medication-related allergy, 41.8% (n=3026) had a BLA. Of the entire cohort, 2,777 (9.4%) patients had a PAL documented on their encounter and females were approximately twice as likely as males to have a PAL (11.6% vs 6.0%; OR=2.17, 95% CI 2.14-2.19). Of those with BLA that was not a PAL, cephalosporin allergies were reported at 12% and carbapenem allergies were reported at less than 1%. Most patients with a PAL (91.7%) had a low-risk allergy (severity not reported or reported as low risk in the EMR). The odds of having a high-risk PAL did not differ by sex (1.1% females vs. 0.6% males; OR=1.17, 95% CI 0.84-1.65). The odds of having another mediation allergy for patients with PAL was about twice as high in females than in males (7.0% female vs. 2.4% males: OR 2.17, 95% CI 1.83-2.57, $p<0.001$).

Comorbidities Associated with Penicillin Allergy Label Presence

There was a positive association between atopic conditions (unadjusted OR = 2.17, 95% CI 1.94-2.43), autoimmune inflammatory conditions (OR=1.84, 95% CI 1.59-2.13), and obesity (OR = 1.51, 95% CI 1.15-1.96) and a PAL. Specific conditions such as asthma, seasonal allergic rhinitis, eczema, Graves' disease, type 1 diabetes mellitus, obesity, multiple sclerosis, rheumatoid arthritis, lupus erythematosus, and Sjögren syndrome were also associated with increased odds of PAL, with ORs ranging from 1.52 to 3.72 ($p<0.05$). Table 5 includes results of the analysis with each comorbidity and correlation with PAL presence.

In the sex stratified models (Figure 6, Supplement M), female sex and ankylosing spondylitis, asthma, eczema, lupus erythematosus, myasthenia gravis, rheumatoid arthritis, seasonal allergic rhinitis, and Sjögren syndrome were associated with increased odds of PAL, with unadjusted ORs ranging from 1.39 to 3.29 ($p<0.05$). In males, asthma, multiple sclerosis, and obesity were associated with PAL with unadjusted ORs ranging from 1.86 to 4.05 ($p<0.05$), while other conditions were not statistically significant in either sex.

Multivariable Models

In multivariable logistic regression analysis, several factors were independently associated with the presence of a penicillin allergy label (PAL). Female sex was associated with higher odds of PAL compared with male sex (OR = 1.47, 95% CI 1.34–1.62, $p < 0.001$). Atopic conditions were also associated with increased odds of PAL (OR = 1.46, 95% CI 1.29–1.66, $p < 0.001$), whereas autoimmune and the metabolic

(obesity) condition categories were not (Table 3). Age effects were heterogeneous: patients aged 65–80 years did not have a significant association with PAL presence, whereas patients over 80 years had significantly higher odds (OR = 1.16, 95% CI 1.02–1.32, $p < 0.05$). The number of other reported medication allergies was strongly associated with PAL with the reference category being 0-1 allergy: having 2 allergies was associated with a 10.44-fold increase (95% CI 9.28–11.74, $p < 0.001$), and 3 or more allergies with a 13.33-fold increase (95% CI 11.72–15.16, $p < 0.001$).

Intersectional Variables (PROGRESS Factors)

Due to extensive missing data PROGRESS factors, these variables were excluded from analyses and are reported descriptively only, as inclusion or imputation would introduce bias. Gender Identity was missing for 99.6% of patients; the remaining 0.6% identified as cisgender male or female, transgender male or female, or non-binary. Education level was missing for the entire cohort. Language was unreported in 67.4%; 28.5% reported English, 0.7% Portuguese, 0.3% Spanish, 0.3% Cantonese, and 2.7% other. Ethnicity was missing in 92.2%; 2.5% identified as White (North American or European), 0.4% as South or East Asian, and 4.9% as other. Religion was missing in 89.1%, with diverse beliefs comprising the remaining 10.9%. A summary of intersectional and sociodemographic variables is presented in Table 6.

Discussion

In this cross-sectional study of over 29,000 adults attending an ambulatory care hospital, we assessed the association between sex and PAL and explored correlates of PAL focusing on differences by sex. Consistent with previous literature, females were twice as likely to have a PAL as males and more often reported multiple medication allergies. Most PALs were reported as low risk (91.7%), and sex did not significantly influence severity. In multivariable analysis, female sex, atopic conditions, older age (>80 years), and a higher number of other medication allergies (greater than 1 allergy) were independently associated with PAL, whereas autoimmune and metabolic conditions were not. These associations may reflect underlying immune mediated predisposition, cumulative medication-related exposure risk to allergic reactions, and age-related differences in allergy risk, recognition, or documentation.

These findings on sex differences and allergy-related characteristics contextualize prior studies on PAL prevalence and its association with sex. Three studies validating PAL through Penicillin Skin Testing (PST) reported mixed sex-related results by age group but lacked covariate adjustment, limiting validity. In a US preoperative cohort, Park et al. found female sex associated with higher odds of positive PST in adults

(OR = 3.6, 95% CI 1.9–7.2, p < 0.001), though factors such as other medication allergies, age, and comorbidities were not assessed (22). Fox and Park found no sex difference among patients under 18 years (p = 0.52), suggesting possible age-related or unmeasured confounding effects (73); however, this present study included only adults. Similarly, Voelker et al. found adult females were ten times more likely to have a positive PST in an inpatient setting (23). While PST is the gold standard for penicillin allergy validation, these studies may overestimate prevalence, especially among low-risk patients, due to false positives (149). This study builds on prior work by examining outcomes by sex and identifying factors contributing to allergy risk. Stratifying penicillin allergy risk is clinically important, as inaccurate labels increase use of broad-spectrum antibiotics, resistant infections such those caused by MRSA, adverse events such as *C. difficile* infection and MRSA, overall healthcare costs, and morbidity (12,149). Incorporating intersectional variables such as sex into validated risk tools like PEN-FAST (150), can enhance antimicrobial stewardship and promote equitable care.

In a model considering comorbidities, asthma was strongly associated with PAL in females and males, while seasonal allergic rhinitis and eczema were significant only in females. Autoimmune inflammatory conditions, notably systemic lupus erythematosus, myasthenia gravis, and rheumatoid arthritis, were linked to PAL in females, whereas most autoimmune conditions were not significant in males. Obesity was associated with PAL in both sexes in this study, reaching significance in males (OR 1.86, p<0.05), consistent with a brief report of the US National Inpatient Registry, which found obesity increased the odds of PAL (OR 1.55, 95% CI 1.54–1.56, p<0.001) (151). Similarly, a cohort of pregnant patients by Buckey et al. reported that atopic conditions including rhinitis, asthma, and eczema were associated with higher PAL prevalence in multivariable analysis (OR 1.55 vs. none, p<0.0005) consistent with our work which found these conditions to be significantly associated with PAL in females, with asthma also significantly associated in males (152). Although Buckey et al. also reported lower PAL likelihood in Black patients (OR 0.59, p<0.0005), prior systematic review evidence from our team found that most patients included in delabeling studies were White (133), highlighting potential risk of selection bias. In our cohort, ethnicity data were largely missing, and most reported patients were White, limiting assessment of race and PAL risk. Overall, these findings suggest a complex set of contributors to PAL risk in addition to sex, although effect sizes differ between males and females.

Lastly, we aimed to explore whether severity of illness differed in patients with PAL, given prior studies linking PAL to worse clinical outcomes (7,153). Although we initially planned to use an adjusted

National Early Warning Score (NEWS) (154) as a marker of clinical severity, this variable was calculable for only 2% of patients. Consequently, we could not reliably assess the relationship between illness severity, PAL, and sex. Future studies with more complete and validated measures of clinical severity are needed to clarify whether PAL is associated with differences in illness severity and whether these effects vary by sex.

There are several limitations to this study. The cross-sectional design precludes determining whether comorbid conditions preceded PAL, limiting causal inference. PALs and allergy-related data may change over time with testing, delabeling, or documentation updates, which cross-sectional analyses cannot capture. Allergy severity was grouped into high ("High" and "Moderate") and low ("Null" and "Low") risk, though the "Null" category may reflect incomplete documentation rather than true low risk, introducing misclassification bias. The absence of standardized definitions for severity levels may create subjective interpretation by clinicians. Small sample sizes for individual conditions required grouping into broader categories, possibly masking condition-specific effects. The dataset lacked PROGRESS variables (76) and information on age of PAL onset or relevant genetic polymorphisms (155–157), limiting intersectional analyses. Comorbidity data could not be validated, introducing potential information bias. Longitudinal studies with validated, detailed data are needed to clarify PAL drivers, social, and biological interactions.

Conclusion

This study adds to our understanding of the relationship between a person's sex and PAL presence in a large ambulatory adult population within a healthcare system that provides publicly funded health care. In this cross-sectional study, approximately one in ten patients had a PAL, the majority of whom were female. Most PALs were classified as low risk, with the risk category of the allergy (low or high risk) not differing by sex. In the multivariable model, female sex, atopic conditions, older age, and a higher number of other medication allergies appear to be key independent predictors of PAL, whereas autoimmune and metabolic conditions were not significantly associated. These findings suggest that PAL may be influenced by multiple independent predictors. Future research using a longitudinal, prospective design, as well as validated methods for allergy assessment, such as oral challenge for low-risk patients and PST for higher risk patients, along with as collection of comprehensive demographic information may better inform equitable and evidence-based approaches to allergy assessment and antimicrobial stewardship practices.

Chapter 5 : Assessing Whether Sex is an Effect Modifier of the Association between Penicillin Allergy Label Status and Antibiotic Utilization: A Cohort Study

Overview

Background: Appropriate antibiotic use is central to infectious disease management, yet penicillin allergy labels (PALs) often lead to deviation from first-line therapies and poorer infection-related outcomes. The higher prevalence of PALs and greater antibiotic exposure observed in females highlights the importance of determining whether PAL status influences antibiotic selection differently across sexes.

Aim: This study aimed to assess whether sex modifies the association between PAL status and antibiotic prescribing including effects on antibiotic class, use of second-line agents when beta-lactams are indicated, and antibiotic utilization patterns among patients with a PAL.

Methods: This retrospective cohort study included adults (≥18 years) from a single ambulatory care hospital urgent medicine clinic in the Province of Ontario, Canada (2015–2024). The main exposure was the presence of a PAL with a primary outcome of antibiotic administration during a first encounter. Among those receiving antibiotics, secondary outcomes included antibiotic class selection and the use of beta-lactams for those with conditions in which beta-lactams were preferred first-line agents. Multivariable logistic regression was used to test sex as an effect modifier by adding a multiplicative interaction term between PAL and sex to the model while adjusting for age and comorbidities. Firth's bias-reduced regression was applied when separation occurred, or small sample sizes were present.

Results: Among 29,645 patients, 2,777 (9.4%) had a PAL and 2,908 (9.8%) received an antibiotic at first encounter. Patients with PAL had similar comorbidity distributions to those without, except for a higher prevalence of COPD. After adjusting for potential confounders, PAL was associated with increased odds of antibiotic use (adjusted OR 1.25, 95% CI 1.09–1.43) and female sex was associated with lower odds of use (OR 0.72, 95% CI 0.67–0.78). PAL and sex were also independently associated with class-specific antibiotic use. Sex did not significantly modify the association between PAL and antibiotic use (interaction p-value = 0.27) or PAL and class-specific antibiotic use (interaction p-value ranges = 0.06-0.99) or guideline-recommended therapy (interaction p-value = 0.85). Among patients for whom beta-lactams were guideline-recommended, no factors, including PAL, were significantly associated with beta-lactam use.

Conclusion: Sex did not appear to modify the association between PALs and overall antibiotic use or class-specific selection. Nonetheless, PALs and sex were independently associated with altered antibiotic

use and selection of antibiotic class. These findings highlight the independent association of PALs and sex on antibiotic selection and underscore the importance of accurate allergy assessment and delabeling to support guideline-concordant prescribing.

Background

Appropriate antibiotic selection is an essential component to the management of infectious diseases, with beta-lactams, particularly penicillins, being frequent backbones in therapeutic regimens. Beta-lactam antibiotics are often first-line agents for conditions such as acute otitis media, sinusitis, community-acquired pneumonia, streptococcal pharyngitis, and many skin and soft tissue infections (142,158–160). Although empiric and targeted therapy may be clear based on the infectious disease or pathogen parameters, the appropriateness of antibiotic choice is shaped by a variety of clinical and demographic factors. One notable factor is the presence of a penicillin allergy label (PAL) which frequently prompts the use of second-line, often suboptimal antibiotics, potentially leading to poorer clinical outcomes, elevated healthcare utilization, and increased costs (7,11,12,161,162). Further, PALs are often inaccurate with fewer than 10% of patients with a reported allergy label being truly allergic upon formal evaluation (163,164). Although the presence of a PAL is known to impact patient outcomes, emerging evidence suggests that the impact of PAL status on antibiotic selection may not be uniform across all patient subgroups (69,152,165). Specifically, biological sex could serve as an effect modifier, altering the strength or direction of the association between PAL status and antibiotic choices. This is plausible through several key pathways.

First, sex may influence the likelihood of receiving a PAL. Previous literature suggests that females are 2 to 3 times more likely to have a PAL compared to males and that healthcare utilization is higher among females (22,77,133,166). However, from an intersectionality perspective (75), sex may not be an isolated factor in the association with antibiotic utilization in those with PAL; other social and structural determinants such as gender, race or ethnicity, socioeconomic status, and access to care are important to consider, where available, which may further influence both the likelihood of receiving a PAL and patterns of healthcare utilization.

Second, females have a higher prevalence of drug hypersensitivity and differences in immune reactivity including a higher risk of type 1 hypersensitivity presentations (167,168). This difference in

immune mediated disease response has been suggested to be related to sex hormones across innate immune cells, such as dendritic cells (169), and in the mucosal microenvironment of epithelial cells, such as with Toll-like receptor (TLR7) expression in the pathogenesis of systemic lupus erythematosus, which has a significant female prevalence (169).

Third, sex may influence how prescribers choose antibiotics. For example, prescribers and patients may avoid certain antibiotics in reproductive-age women to minimize teratogenic and adverse outcome risks (170,171). Moreover, population-based studies show that females are more likely to receive antibiotics than males (172–174).

Fourth, sex-related differences in pharmacokinetics and pharmacodynamics may impact antibiotic selection driven by differences in gastric pH, gastrointestinal motility, drug distribution, plasma protein binding, and metabolic enzyme pathways (83). Reviews consistently describe sex-related differences in pharmacokinetics, including slower gastric emptying and higher average CYP3A4 activity in females (82,83). Further, sex differences have been observed in hepatic metabolism of medications such as propranolol due to sex discordant CYP 2D6 metabolism, and ethanol through CYP 2E1 metabolism (82). Notably, adverse event rates may differ by sex (77,82) with fluoroquinolones among the antimicrobial classes most frequently implicated in sex-related safety signals. Observational and postmarketing data suggest that females more commonly experience cardiac conduction abnormalities, whereas males, particularly older males, have a higher incidence of fluoroquinolone-associated tendon rupture (175,176).

Furthermore, prescribing patterns may also reflect gendered norms (both for the clinician involved in the care and the individual receiving care), risk perceptions, and healthcare-seeking behaviours, which can vary across populations and intersect with factors such as education, cultural context, and healthcare access. Taken together, these findings underscore the importance of applying an intersectional framework to current literature that shows a female predominance in PAL presence, such as PROGRESS-Plus, to better understand how overlapping determinants (e.g., gender or sex, race or ethnicity, socioeconomic status, and age) shape both the presence of PALs and downstream antibiotic-related outcomes, ultimately informing more equitable and precise approaches to antimicrobial stewardship.

Prior literature indicates that PAL status may affect both the likelihood of antibiotic treatment and antibiotic class selection, and that these associations may plausibly differ between males and females due to known sex-related differences in immunologic response, pharmacokinetics, and prescribing practices.

The primary objective of this retrospective cohort study was to assess the association between PAL status and antibiotic administration and to evaluate whether sex modified this association. Where no evidence of effect modification by sex was identified, we evaluated the independent association between PAL and sex with antibiotic use. The secondary aims were to determine, among those who are prescribed an antibiotic: whether sex modified the relationship between PAL status and the class of antibiotic administered, and whether a beta-lactam was administered in those with a clear indication at admission, particularly for infections where beta-lactams are first-line agents.

Methods

Study Design and Source Population

This retrospective cohort study utilizes de-identified electronic medical record (EMR) data from adults (≥18 years) with an encounter in an urgent medicine clinic at a single ambulatory care hospital in a large urban metropolis in Ontario, Canada, from 2015-2024. Exclusion criteria were non-Urgent Medicine Clinic encounters and patients who were missing sex as a variable on the EMR. Non-Urgent Medicine Clinic encounters (procedure room and surgical encounters) include cases that are not intended for the short-stay medical unit, which provides urgent assessment, investigation, and management of medical conditions.

This study received ethics approval from Women's College Hospital (REB #2024-0055) and the University of Waterloo's Clinical Research Ethics Board (#45818). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline and Enhancing the Quality and Transparency of Health Research (EQUATOR) STROBE checklist for cohort studies were applied to this manuscript (144,177).

Exposure, Effect Modifier, and Outcome Definitions

The main exposure, PAL, was defined as a binary variable based on any documented allergy to a penicillin as recorded in the EMR. Free-text allergy entries were standardized to a set of penicillin and non-penicillin β-lactam terms prior to analysis by a pharmacist with expertise in infectious diseases. All groupings by antibiotic classes and categories are found in Appendix K and L.

The primary outcome was inpatient antibiotic administration for the patient's first encounter to the clinic, defined as any verified antibiotic utilization on the medication administration record (MAR) during

that encounter (i.e., a binary variable indicating antibiotic administered or no antibiotic administered). Use of the MAR as the source for administered antibiotics follows prior validation work showing it to be appropriate source for hospital antibiotic administration verification (178), making it the most suitable source of antibiotic administration information.

Two main secondary outcomes were assessed in sub-cohorts. First, among patients with an antibiotic on the MAR, each antibiotic class was defined as a binary variable. There was a total of 11 antibiotic classes assessed as individual secondary outcomes. Antibiotics included within classes are listed in Appendix O; infrequent and miscellaneous agents were collapsed into an "Other" category. Second, for patients with selected infectious diagnoses whereby beta-lactams are guideline-recommended first-line therapy, a binary indicator (yes/no) for beta-lactam utilization (i.e., guideline concordant therapy) was defined as a secondary outcome. Guideline concordance was assessed using established definitions for first-line beta-lactam therapy as specified in guidelines described in Appendix P. Infectious disease-related reasons for an encounter where beta-lactams were considered first-line therapy included: febrile neutropenia, community-acquired pneumonia, diabetic foot infection, skin/soft tissue infection, targeted methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteremia, or culture-guided therapy. Infectious disease diagnoses on first encounter were based on ICD-10-CA Version 2019 by the World Health Organization (179) and can be found in Appendix Q.

Sex assigned at birth (binary: male, female), the proposed effect modifier, was defined from the EMR field for sex. Because counts for intersex/unknown entries were <6, those levels were excluded from the analyses.

Potential Confounding Variables

Conditions that have been linked with PAL status as described in previous literature including atopic conditions, autoimmune inflammatory conditions, and obesity are included as covariates in the multivariable models (binary variables with a reference category of no condition) (69,180). Conditions with potential to be associated with increased infection burden that have not been otherwise considered in the categories described above, such as diabetes mellitus (type I or type II) (181,182), chronic obstructive pulmonary disease (183), cancer (hematologic malignancy or solid tumor cancer) (184), chronic kidney disease (185), cirrhosis (186), and heart failure (183), were also considered as potential confounding

variables and were included in the multivariable regression model if substantial imbalance was observed between those with and without a PAL.

Statistical Methods and Analyses

Descriptive statistics summarized baseline characteristics stratified by PAL status and sex. Categorical variables were reported as counts and percentages, and continuous variables were reported as means with standard deviations or medians with interquartile range. Absolute standardized differences (ASD) assessed baseline imbalance between those with versus without a PAL. Variables with ASD >0.10 were considered substantially imbalanced and adjusted for in multivariable models (187,188).

For the primary analysis, a multivariable logistic regression model assessed the association between PAL and antibiotic utilization, with sex (male as reference category) evaluated as an effect modifier using a multiplicative interaction term (PAL*SEX) in the total cohort (base model). A fully adjusted model additionally included baseline variables with ASD >0.10 and covariates known to be associated with PAL or infection risk. Covariates included age (<65 [reference], 65–80, >80 years), number of allergy labels (0-1 [reference], 2, 3+), atopic conditions (binary), autoimmune inflammatory conditions (binary), and metabolic conditions (binary).

Secondary analysis used a similar modeling approach to examine sex as an effect modifier of the association between PAL status and antibiotic class (11 classes analyzed separately), among patients who received an antibiotic. Among patients with antibiotic use and diagnoses for which beta-lactams were considered first-line therapy, multivariable logistic regression was used to assess the association between PAL status and beta-lactam use (binary) versus other antibiotic classes, with sex evaluated as an effect modifier in both base and adjusted models. The adjusted model included the same covariates as the primary analysis (variables with ASD >0.10 and covariates associated with PAL presence), excluding infectious disease-related diagnoses as infection was the reason for referral.

To evaluate effect modification by sex, we prespecified formal interaction testing using a product term between PAL and sex in multivariable models, consistent with recommended approaches in pharmacoepidemiology (189,190). A likelihood ratio test assessed the significance of the multiplicative interaction, with a p-value <0.05 indicating effect modification. In the absence of a statistically significant interaction, the interaction term was removed from the model and the independent associations between PAL status and sex with the outcomes of interest were reported. Firth's bias-reduced logistic regression

was applied in the presence of separation or small sample sizes. Model assumptions and diagnostics were checked using standard methods. Analyses were conducted in R Version 4.3.3 (R-Studio) (148,191).

Results

Population Demographics

The source population included 29,645 patients, of whom 2,777 (9.4%) had a documented PAL. Patients with a PAL were predominantly female (74%) compared to those without a PAL (Table 7). The overall mean age was 54.7 years (SD=19.8), with mean age by sex of 53.9 years (SD=20.1) among females and 55.8 years (SD =19.3) among males. Across the full cohort, the most common comorbidities were coronary artery disease (32.8%), hypertension (27.2%), and diabetes (13.8%). This ordering was consistent among males and females without a PAL and in males with a PAL; however, among females with a PAL, asthma (15%) replaced diabetes as the third most common condition. Absolute standardized differences for the most common medical conditions associated with increased infection risk were <10% when comparing patients with versus without PAL, except COPD (ASD 0.11). Notably, other conditions associated with increased infection risk in the literature, including diabetes mellitus, cancer, chronic kidney disease, cirrhosis, and heart failure, did not demonstrate meaningful imbalance by PAL status.

PAL, Sex and Antibiotic Use

Among the 2,777 patients with a PAL, 343 (12.4%) received an antibiotic, compared with 2,565 (9.5%) of 26,868 patients without a PAL. In the base model, PAL status was associated with an increased odds of antibiotic use (OR 1.34; 95% CI 1.16-1.56), while female sex was associated with a lower odds (OR 0.72, 95% CI 0.67-0.78); the interaction term between PAL and sex was not statistically significant (p=0.27).

In the adjusted model, including age, atopic, autoimmune inflammatory, and metabolic conditions, allergy frequency, and presence of COPD, the interaction between PAL and sex remained non-significant (p=0.12) (Appendix R). Therefore, the interaction term was removed from the model. In the final adjusted model without an interaction term, PAL remained associated with increased antibiotic use (OR 1.25, 95% CI 1.09-1.43) and female sex remained associated with lower odds of antibiotic use (OR 0.73, 95% CI 0.67-0.79) (Table 8).

PAL, Sex and Antibiotic Class

Antibiotic class utilization varied by PAL status and sex (Table 9). Among patients with a PAL, fluoroquinolones were the most prescribed antibiotics (35.4% in females and 30.0% in males), followed by cephalosporins (21.2% and 28.2%), with other antibiotic classes prescribed less consistently by sex. In contrast, among patients without a PAL, penicillins were the most frequently prescribed class (33.6% in females and 35.6% in males), followed by cephalosporins (26.7% and 28.6%), and fluoroquinolones (17% and 19.8%).

Across all antibiotic class-specific models, the PAL*SEX interaction was not statistically significant in either base models (p-value range 0.09-0.99) or adjusted models (p-value range 0.06-0.99). Thus, models excluding the interaction term are presented in Table 10, with interaction p-values provided for reference.

In fully adjusted models, PAL status was associated with lower odds of penicillin use (OR 0.33, 95% CI 0.23-0.48) and a higher odds of non-beta-lactam antibiotic used, including macrolides (OR 2.94, 95% CI 1.96–4.40), fluoroquinolones (OR 2.54, 95% CI 1.96–3.28), tetracyclines (OR 1.66, 95% CI 1.02–2.69), and lincosamidse or glycopeptides (OR 4.50, 95% CI 2.69–7.54). Female sex was associated with a higher odds of use of antibiotics classified as ‘other’ (OR 1.82, 95% CI 1.32-2.52) and lower odds of penicillin (OR 0.73, 95% CI 0.63-0.83), cephalosporin (OR 0.66, 95% CI 0.56-0.77), fluoroquinolone (OR 0.69, 95% CI 0.57-0.82), and folate synthesis inhibitor use (OR 0.53, 95% CI 0.38-0.73). Results from the full models for overall antibiotic use and antibiotic class-specific use are presented in Appendix S and T.

Guideline Directed Beta-lactam-Class Utilization for Select Infections

A total of 394 patients (1.3%) were seen for an infectious disease-related first encounter, among whom 151 (38%) had conditions for which beta-lactams were considered first-line therapy. The PAL*SEX interaction was not statistically significant (p=0.80) and was therefore removed from the model. In both the base model (PAL p=0.24, sex p=0.98) and fully adjusted model (PAL p=0.21, sex p=0.75), neither PAL status nor sex was significantly associated with beta-lactam prescribing in this subgroup. Results from the full adjusted model are presented in Appendix U.

Discussion

This cohort study of about 30,000 patients seen at an Urgent Medicine Clinic found that nearly one in ten patients carried a PAL, with a higher prevalence among females. Although we did not detect effect modification by sex in the association between PAL status and antibiotic use or class selection, PAL and sex were independently associated with antibiotic prescribing patterns.

Consistent with prior literature, PAL status was associated with higher overall antibiotic use and substitution away from beta-lactams, influencing antibiotic selection. Moreover, female sex was associated with lower overall antibiotic prescribing and differences in class selection. This contrasts with prior population-based studies reporting higher antibiotic use among females (192,193), and may reflect fewer infectious diagnoses among females in this particular cohort, increased clinician awareness of sex-based prescribing biases, or incomplete capture of prescriptions provided outside the clinic EMR.

Prior literature has identified gendered diagnostic and therapeutic decision-making, including in chronic pain and atrial fibrillation (194,195), and this study's findings may reflect similar disparities in antibiotic prescribing. These patterns are particularly relevant for antibiotic stewardship, given that more than 90% of PALs can be safely delabeled through structured assessments (165) and beta-lactams remain first-line therapy for many infections (7). In this study, PAL status was associated with lower odds of penicillin use and higher odds of macrolide, fluoroquinolone, tetracycline, and lincosamide or glycopeptide prescribing, consistent with previous studies. Female sex was generally associated with lower odds of several antibiotic classes and higher odds of 'other' antibiotics, largely driven by nitrofurantoin and fosfomycin, likely reflecting management of urinary tract infections, which occur far more frequently in premenopausal women (196).

Avoidance of beta-lactams among patients with a PAL was also associated with increased use of broader-spectrum antibiotics, including macrolides fluoroquinolones, and lincosamides or glycopeptides, which was consistent with previous studies (12,25,197). Importantly these agents have been linked to higher rates of antibiotic resistance and adverse outcomes (153,161,162). These findings reinforce the potential downstream consequences of PAL misclassification and incomplete allergy evaluation.

Among patients for whom beta-lactams were guideline-recommended first-line therapy, no characteristics, including PAL status, were significantly associated with prescribing. While this suggests overall alignment with guideline-based care, the small sample size for this subgroup limits interpretability

and likely has reduced power to detect meaningful differences. More granular evaluation using an intersectional lens that incorporates patient behaviour, clinician decision-making, and contextual prescribing factors is needed.

This study has several limitations. Use of EMR data may have introduced information bias related to incomplete capture of medication histories, allergy documentation, and antibiotic prescriptions, particularly for prescriptions provided verbally or for administration outside the clinic. PAL misclassification is possible if labels were self-reported or unverified. Residual confounding may persist due to unmeasured factors such as provider prescribing behaviours, socioeconomic variables, or prior antibiotic exposure. Antibiotics initiated in the emergency department and tolerated prior to clinic referral may have influenced beta-lactam use and clinician comfort. Lastly, this single-center study limits generalizability and the encounter-level timeframe precludes causal inference. Some sex- and class-specific subgroup analyses were likely underpowered.

Conclusion

In this retrospective cohort study, we did not detect effect modification by sex in the relationship between PAL status and overall antibiotic use or the selection of specific antibiotic classes. However, both PAL status and sex demonstrated independent associations with antibiotic prescribing patterns. These findings suggest that while interaction effects were not present, each factor may have influenced prescribing behavior through distinct mechanisms. Optimizing antibiotic stewardship will require accurate allergy assessment and delabeling, along with awareness of sex-related prescribing patterns, to reduce unnecessary broad-spectrum antibiotic use and promote adherence to evidence-based guidelines.

Chapter 6 : Major Findings, Limitations, Clinical Implications, and Future Directions

Major Findings

PALs remain common in clinical practice despite strong evidence that most individuals labeled as penicillin allergic can safely tolerate penicillin after structured evaluation. This thesis used multiple complementary study designs to examine sex-based differences across PAL reporting, delabeling strategies, and antibiotic use, given that evidence from a small number of studies suggests sex-based variation in PALs, although the findings are inconsistent in prior studies (22,23,89,103,104). Findings from the broader PAL delabeling literature and this thesis support that low-risk delabeling strategies, including DD for non-allergic histories and OC for low-risk allergies, are safe and effective (133,165).

A key aspect of this thesis was to quantify PAL prevalence across populations to better contextualize potential clinical impact and understand what intersectional factors were either correlated with PAL or were absent from the literature. Although reported prevalence ranges from 8% to 25% (8,36,198), estimates consistently cluster around 10% across diverse settings (7,19,37,133). This was supported by both the systematic review and meta-analysis conducted for this thesis (133) and epidemiologic analyses using data from Women's College Hospital. Importantly, this prevalence far exceeds that of true penicillin allergy as over 90% of individuals with a PAL can be successfully delabeled following appropriate evaluation (7,129). The presence of a PAL on a patient's medical record is associated with increased use of second-line antibiotics and adverse clinical and system-level outcomes, stressing the importance of accurate risk stratification and the importance of delabeling where appropriate.

Risk stratification was a major emerging theme to explore in this thesis. Given that approximately 50% of individuals with a PAL met low-risk criteria based on structured tools (133), consideration for strategies to address these allergy labels is both clinically important and potentially addressable in resource limited settings. In the studies synthesized in both the systematic review and the descriptive epidemiologic study in this thesis, among those who underwent OC or risk-based delabeling, over 90% were successfully delabeled with no severe reactions reported, supporting the safety and feasibility of OC in low-risk cases (165). This finding of safety of delabeling for PALs was also corroborated by a systematic review of the literature following advice from the World Health Organization (WHO)'s guideline committee (130).

Despite some variability, definitions of low-risk PAL were largely consistent across studies. Low-risk histories typically included non-severe cutaneous reactions, remote or unknown reactions, intolerance symptoms, prior tolerance, and absence of anaphylaxis or angioedema. This consistency supports the use of standardized history-taking and risk assessment to guide delabeling decisions. Although penicillin skin testing (PST) has traditionally been considered the reference standard, its routine use in low-risk populations may contribute to unnecessary resource use and persistent mislabeling, given the low prevalence of true allergy and modest positive predictive value. As low-risk PALs comprise a substantial proportion of labeled individuals, estimated at over 60% in this thesis (133), these findings support a shift toward streamlined delabeling strategies centered on OC or DD when appropriate.

PAL prevalence was not evenly distributed across sexes. Female sex was independently associated with PAL and with higher comorbidity burden particularly autoimmune inflammatory conditions and atopic conditions as well as the presence of medication allergies. However, sex did not modify the association between PAL and downstream antibiotic use after adjusting for potential confounders, although PAL and sex were independently associated with class-specific antibiotic utilization. These findings highlight the independent association of PALs and sex on antibiotic selection and underscore the importance of accurate allergy assessment and delabeling to support guideline-concordant prescribing.

This thesis also identified gaps in sex- and gender-disaggregated reporting within the PAL literature. While sex was commonly reported, outcomes were rarely stratified by sex, and gender-related variables were largely absent. Where possible, sex-stratified analyses and summaries of intersectional factors were included in this thesis, and limitations due to missing data were explicitly acknowledged. These gaps limit inference regarding equity and reinforce priorities for future research. An example of intersectional data limitations was observed in the systematic review and meta-analysis where approximately 90% of participants were reported as White. This limits generalizability, particularly for cutaneous reactions that may be more difficult to detect in individuals with darker skin tones, as previously described by Diao and colleagues (199). These findings reinforce the need for more inclusive data collection and reporting practices in PAL research.

Predictors of PAL presence and associated outcomes were examined using cross-sectional and cohort study designs. Female sex, older age, atopic disease, and multiple medication allergies were independently associated with PAL presence in the cross-sectional study, which is consistent with prior literature but was examined in a single study design for the first time, to our knowledge. These factors may

reflect increased healthcare contact or reporting rather than true allergy alone, highlighting the value of structured assessment in patients with multiple reported drug allergies. In the cohort study analyses, PAL was independently associated with increased antibiotic use and greater reliance on non-β-lactam and second-line agents, consistent with prior studies. Sex did not modify these associations, suggesting that although sex and PAL status impact outcomes associated with antibiotic utilization, the associations may be independent but equally important for different reasons. These findings emphasize the importance of early intervention through accurate history-taking, risk stratification, and suggestions of delabeling where appropriate.

In summary, PALs remain common, unevenly distributed, and shaped by sex and comorbidity burden; however, our understanding of the full implications may be affected by gaps in data reporting. The higher prevalence of PAL among females, combined with limited sex- and gender-disaggregated analyses and minimal consideration of equity variables, represents a key gap in the literature. Advancing equitable, evidence-informed PAL management will require systematic integration of SGBA frameworks into research and clinical practice.

Limitations

Although the studies across this thesis addressed major questions related to sex-associated factors linked to PAL presence, identified predictors and outcomes associated with PALs, and provided evidence supporting delabeling of low-risk allergies using limited resources, several global limitations remain that must be considered when interpreting the findings and assessing the generalizability of the evidence.

A primary gap identified through the systematic review and descriptive analysis of PAL delabeling in low-risk patients relates to the limited consideration of intersectional variables. Many studies included in the systematic review were conducted in settings with resources, staff, and structures intended to support antimicrobial stewardship initiatives. Additionally, study populations were predominantly White, limiting the applicability of findings to more diverse populations. Ensuring the inclusion of varied racial groups, social factors, data capture, and analysis related to these variables in future research will be critical to improving generalizability. These gaps highlight the need to move beyond single-variable analyses toward examining how overlapping determinants such as race or ethnicity, socioeconomic status, gender, and access to care may interact to influence both PAL status and delabeling outcomes. It is important to consider how these findings generalize to individuals from communities facing systemic barriers as these

individuals may be more likely to carry persistent, inaccurate PALs due to gaps in healthcare access, healthcare trust, communication, and opportunities for reassessment; however, this hypothesis would require prospective validation through future studies to determine intersecting gaps that impact patient outcomes for those with a PAL.

Furthermore, many studies were performed in higher-income countries with resource-rich healthcare systems, access to allergy specialists, supervised oral challenge protocols, and antimicrobial stewardship infrastructures capable of supporting proactive allergy review that may not be available in resource-limited settings. Although the descriptive analysis provides evidence that single-dose amoxicillin oral challenge protocols may be effective, implementation may still be challenging in settings where drug availability is limited and where there is insufficient access to trained clinicians or resources to manage potential ADRs. Therefore, an individual's place of residence may significantly influence the likelihood of both PAL persistence and successful delabeling given that individuals that reside in areas with resource constraint such as remote and rural regions but also lower income regions around the globe may potentially experiencing reduced access to evidence-informed interventions.

Another important limitation is the heterogeneity in effect measures for proportional meta-analyses of direct delabeling and oral challenge studies. This variability limits comparability across studies as well as settings and complicates the development of standardized, globally applicable delabeling protocols, thereby challenging the creation of systematic approaches that can be widely adopted across diverse healthcare settings and populations. This may also speak to the need to consider intersectional factors in standardized approaches, for example some of the language used in assessment frameworks may not be equally applicable across groups defined by language, health literacy, or cultural context. To address this gap, a co-designed approach with patient populations at the centre of an intervention would be required to generate tailored risk stratification tools that account for social and structural determinants.

Although sex was frequently reported as a descriptive variable in studies evaluating penicillin allergy delabeling and predictors of PAL presence, it was rarely examined as a stratified or effect-modifying variable across studies external to those conducted in this thesis, limiting the capacity to describe similarities or differences across studies. Moreover, gender identity, sociocultural factors, and differences in healthcare access were not captured in the studies included in the background of this thesis or in the systematic review conducted in Chapter 2, restricting interpretation of observed sex-based differences and their relevance across diverse populations.

In the cross-sectional and retrospective cohort studies included in this thesis, multiple covariates were incorporated into multivariable logistic regression models to better characterize predictors and outcomes associated with PAL presence, with sex examined as a key covariate in the cross-sectional analysis and as a potential effect modifier in the cohort study. However, limited availability of data on other intersectional variables, such as race, socioeconomic status, and social capital precluded their inclusion and limited further exploration of factors associated with PAL status.

Additionally, clinician-level factors, including prescribing preferences and local provider culture were not captured in any of the analytic studies. Future research incorporating qualitative methods, such as focus groups or questionnaires with thematic analysis, may help elucidate clinician-related barriers and facilitators influencing antibiotic prescribing decisions in patients with PALs. Although co-design with patients was sought for the protocol of the systematic review and this feedback informed the systematic review and meta-analysis, inclusion of the patient voice was missing across the remaining studies in this thesis, and it would, therefore be imperative to consider patient engagement in future research focused on application of these findings to practice. Both health care provider- and patient-level factors may be shaped by social position, cultural norms, and systemic biases, generating hypotheses that communication, trust, and shared decision-making in PAL assessment may differ across intersecting identities and influence delabeling uptake. This would be best studied in a prospective approach whereby clinician-level and patient-level factors around intersectionality are included in the analytic framework.

Given that the epidemiologic studies conducted as part of this thesis relied on administrative databases, limitations related to study design must also be acknowledged. Observational analyses that rely on retrospectively collected information and administrative data are susceptible to misclassification of allergy histories, incomplete documentation of reaction severity, and residual confounding that may not have been captured such as provider culture, language barriers, and accessibility and barriers to visiting a health care provider for each individual patient.

Finally, antibiotic prescribing outcomes in the retrospective cohort study were evaluated within a single regional health system and a unique ambulatory care hospital setting. Prescribing practices, guideline adherence, and antimicrobial availability may differ substantially across jurisdictions, limiting external validity. Collectively, these limitations underscore the need for standardized reporting, integration of intersectional variables into future analyses, and prospective, multi-center studies to support equitable and globally scalable approaches to penicillin allergy delabeling. Future research should explicitly

incorporate intersectionality-informed methodologies to test these hypotheses and identify modifiable drivers of inequities in PAL labeling and management.

Clinical Implications

The findings from the studies across this thesis support factors that can improve PAL risk stratification and delabeling as well as understand predictors that may be correlated with PAL presence and its outcomes while also considering sex as an important factor across the research. A risk-stratified approach to PAL assessment in ambulatory outpatient settings has the potential to significantly improve antibiotic utilization since beta-lactams are often first-line and highly tolerated medications for various infectious diseases.

For patients with a history of confirmed IgE-mediated reactions, such as anaphylaxis within the past 10 years, PST remains the most appropriate method to assess the PAL. However, for patients with low-risk PAL histories, OC provides a definitive and resource-sparing method that can be carried out quickly to assess penicillin tolerability. In contrast, patients with severe delayed hypersensitivity reactions (e.g., Stevens–Johnson syndrome or drug rash with eosinophilia and systemic symptoms) are often instructed to avoid the entire β-lactam class due to risk of life-threatening hypersensitivity on re-exposure. Implementing frameworks that embed DD and OC into evaluation pathways for PALs in ambulatory care could enable delabeling of a substantial proportion of PALs using limited resources, allowing specialized allergy services to focus on complex cases.

The higher prevalence of PALs among females underscores the importance of considering intersectional factors that may be associated with PAL presence. Female sex was independently associated with PAL and distinct comorbidity patterns; however, sex did not modify the association between PALs and antibiotic prescribing or class selection. This suggests that PALs themselves, rather than sex, drive deviations from guideline-recommended therapy, reinforcing the clinical value of delabeling interventions across all patient groups. Other predictors for PAL presence can be considered for integration into clinical decision tools such as the PEN-FAST (104,115) score and other algorithms (65,200) to provide a more thorough understanding of potential factors that correlate to PAL presence.

The limited reporting of sex, gender, and other relevant covariates in existing studies creates limitations in understanding the factors that could contribute to both risk of penicillin allergy labeling and outcomes that may differ by sex for those with a PAL. Integrating OC-based delabeling into routine ambulatory care pathways may improve timely access to first-line β-lactam therapy, reduce unnecessary use of second-line agents, and mitigate downstream consequences such as adverse drug events and antimicrobial resistance.

Future Directions

When considering assessment of PALs and understanding predictors and outcomes associated with PAL presence, future research could consider evaluating scalable, equity-oriented study designs for PAL assessment in ambulatory care settings including community pharmacies and primary care offices. These environments have clinicians who are often equipped with specialized skills for assessment of hypersensitivity reactions and provision of first aid, given that they are settings where vaccines and medications may be administered. One limitation to creating a clinic in primary care or community pharmacies would be time constraints; therefore, specialized funding for these types of clinics to support access would be important to consider.

The piloting of a patient self-referral PAL assessment clinic embedded within a family health team, with particular emphasis on equity-deserving populations and those who require a β-lactam in a pressing manner can be considered. This pilot study would integrate virtual education and risk stratification interventions with streamlined in-clinic OC for eligible patients, facilitated through referral pathways from primary care providers. Sharing standardized documentation following OC evaluations with primary care providers would support continuity of care and sustained delabeling given that records would be updated in the primary care team's clinic notes. The proposed pilot would use a multidisciplinary team with expertise in drug allergy, infectious diseases, antimicrobial stewardship, and knowledge implementation. In addition, this pilot program would include structured patient engagement to ensure that patient-centered outcomes are the focus. Key outcomes would include delabeling rates, patient satisfaction, safety, and feasibility. If successful, the model could improve access to β-lactam therapy, reduce unnecessary antibiotic escalation, and lessen pressure on specialty allergy services.

Outside of this proposed pilot clinic, future research that more deliberately incorporates sex- and gender-related factors in pharmacotherapy and drug hypersensitivity assessment would provide a better understanding of factors that may differentially impact patient care and outcomes. Routine collection and reporting of sex- and gender-disaggregated data, alongside relevant intersectional variables may enable more precise evaluation of patient related risks for adverse outcomes, optimize medication effectiveness, and strengthen the evidence base guiding equitable medication utilization. This basis for incorporating sex- and gender-related factors into pharmacotherapeutic research can extend beyond the bounds of infectious diseases and encompass all pharmacotherapy to better understand the effectiveness and safety of medications across all populations.

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Figures

Figure 1: Random Effects Meta-Analysis of Randomized Controlled Trials

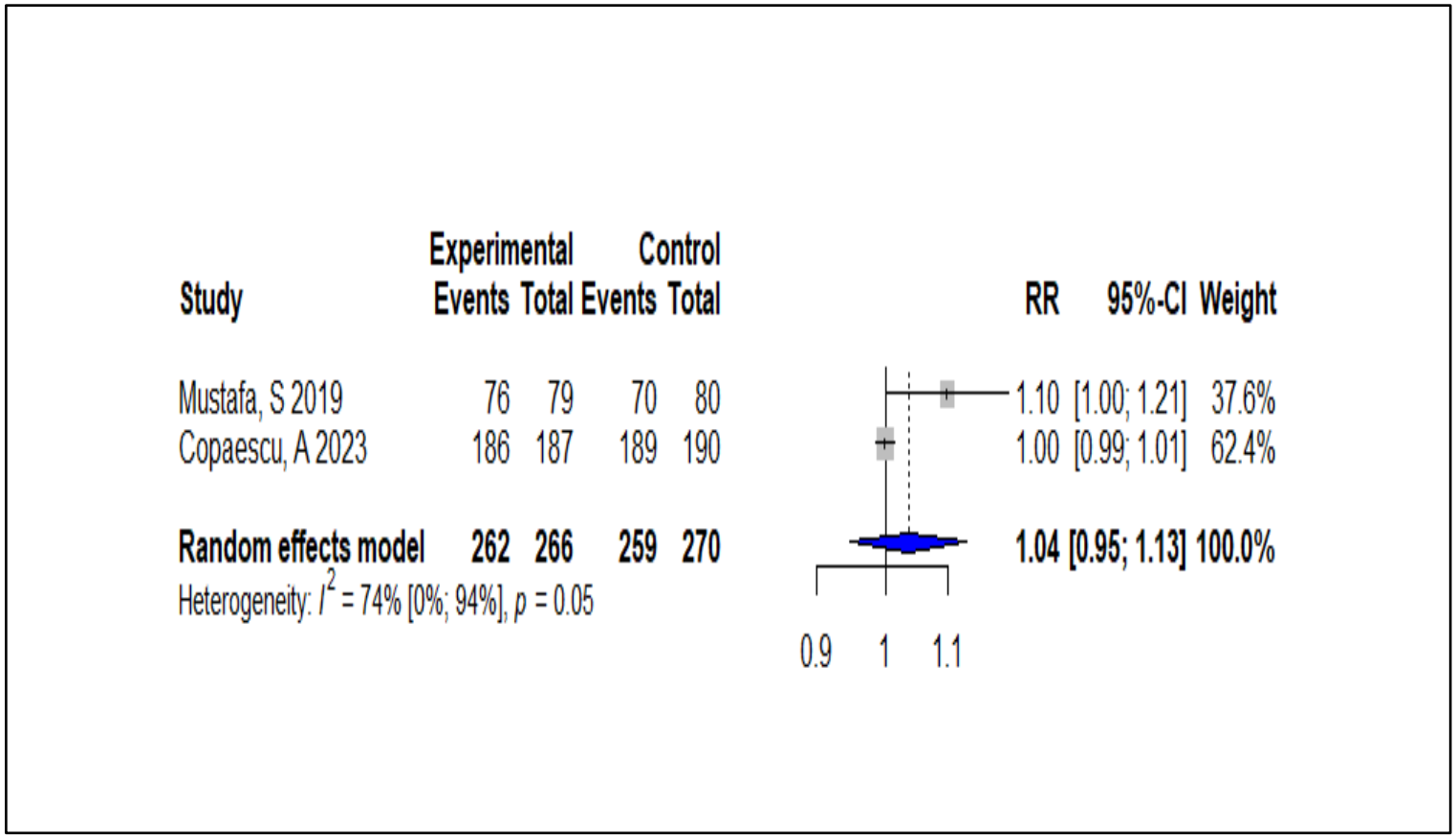
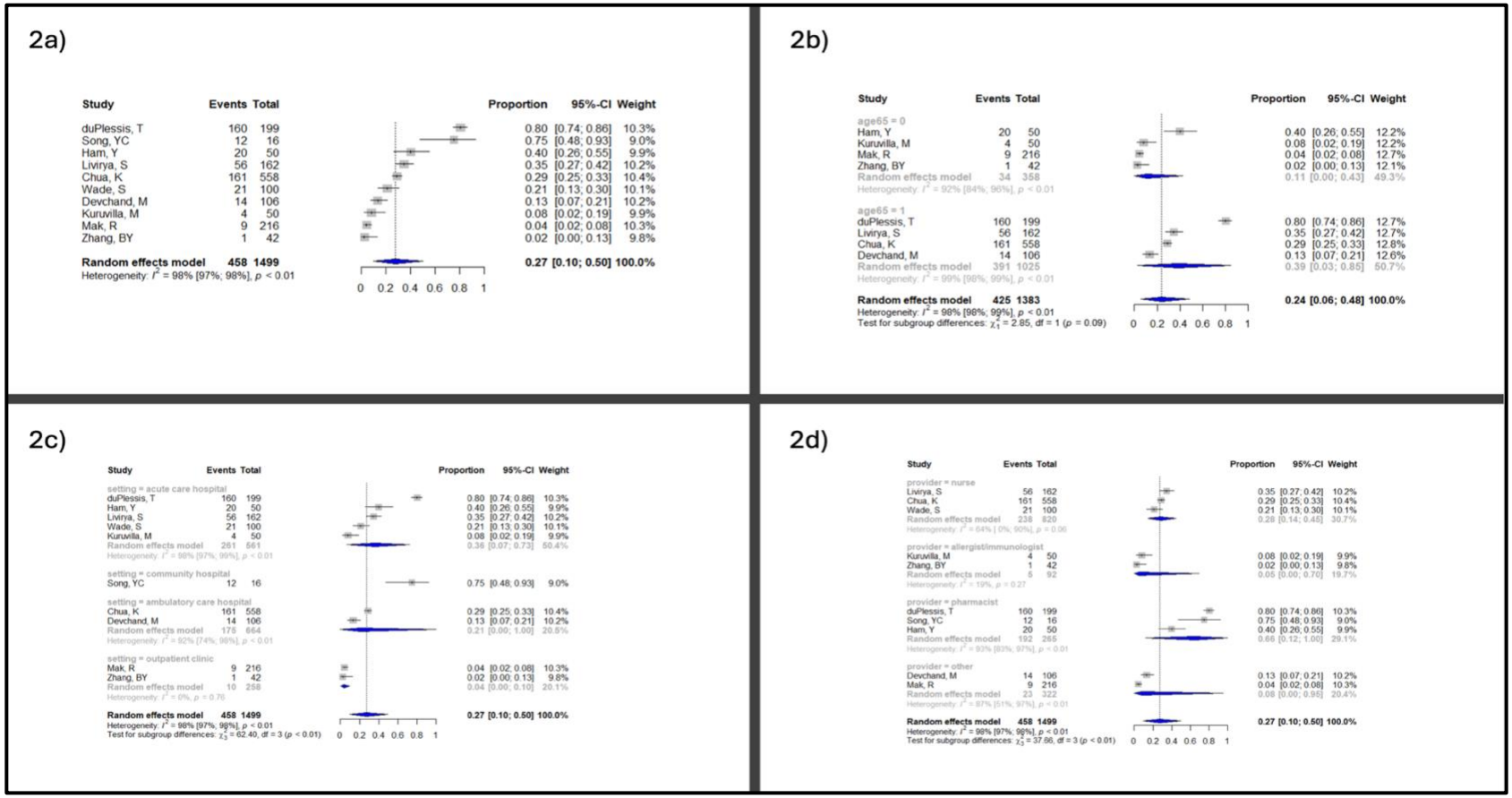
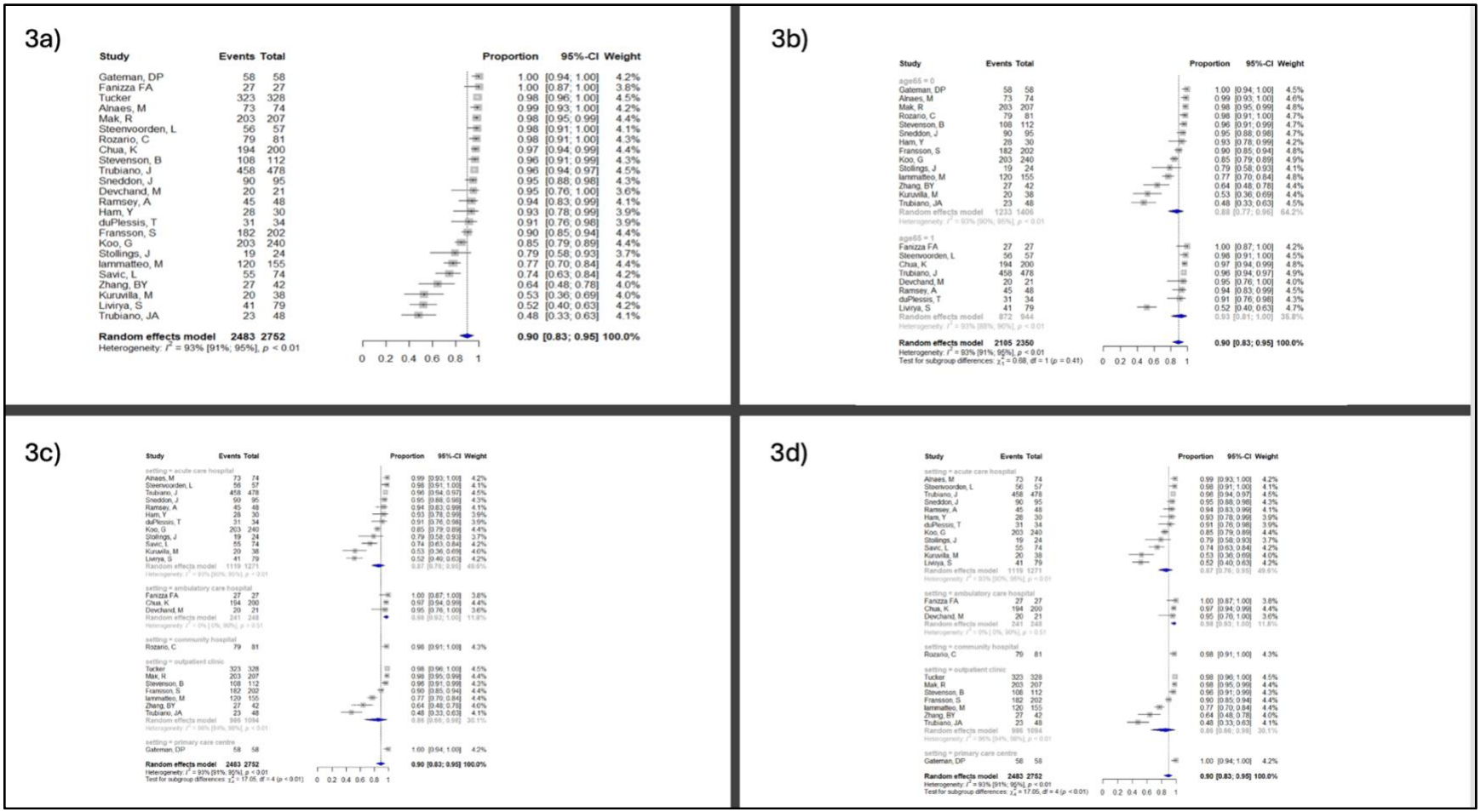


Figure 2: Meta-Analyses for Studies with Direct Delabeling Interventions



Legend 1: Figure 2a) Random effect meta-analysis of all studies with direct delabeling interventions; Figure 2b) Subgroup Meta-Analyses by Age, Figure 2c) Subgroup Meta-Analyses by clinical setting; Figure 2d) Subgroup Meta-Analyses by Provider

Figure 3: Meta-Analyses of Quasi-Experimental Studies Including Oral Challenge Interventions



Legend 2: Figure 3a) Random effect meta-analysis of all quasi-experimental studies with oral challenge interventions; Figure 3b) Subgroup Meta-Analyses by Age, Figure 3c) Subgroup Meta-Analyses by clinical setting; Figure 3d) Subgroup Meta-Analyses by Provider

Figure 4: Random Effects Meta-Analysis for Sex Disaggregated Oral Challenge Outcomes

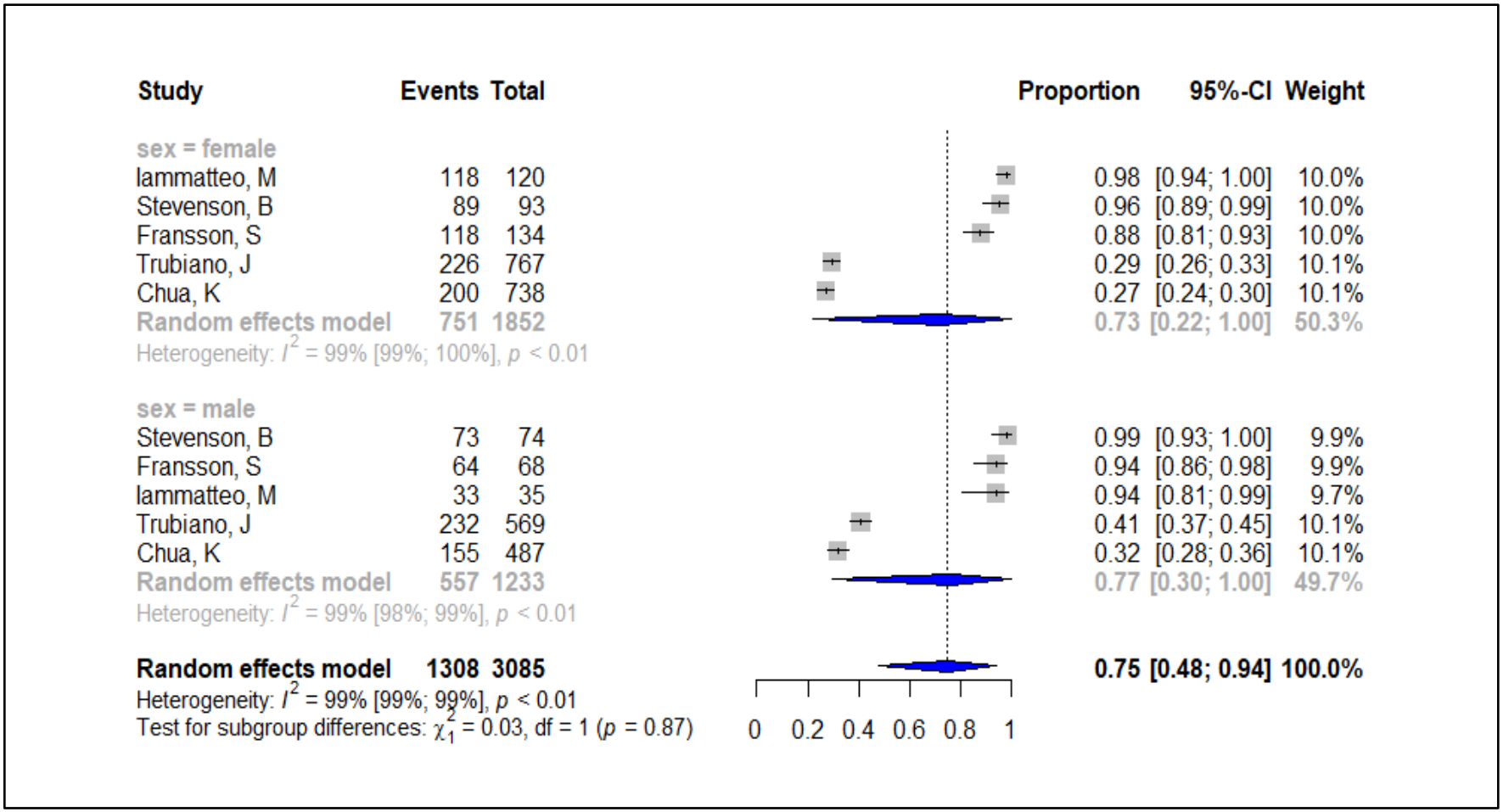


Figure 5: Proportion Meta-Analysis of Oral Challenge Reactions

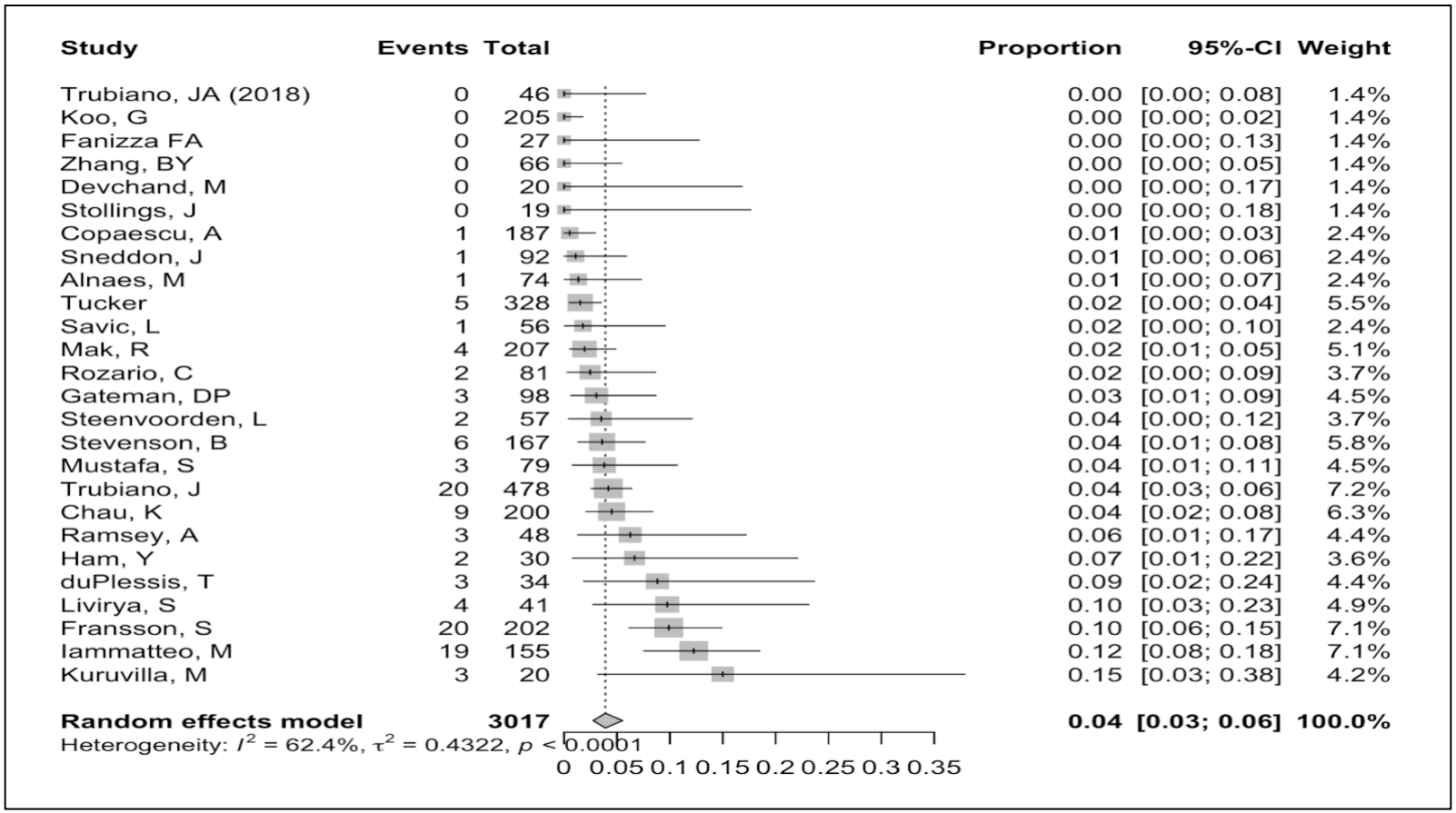
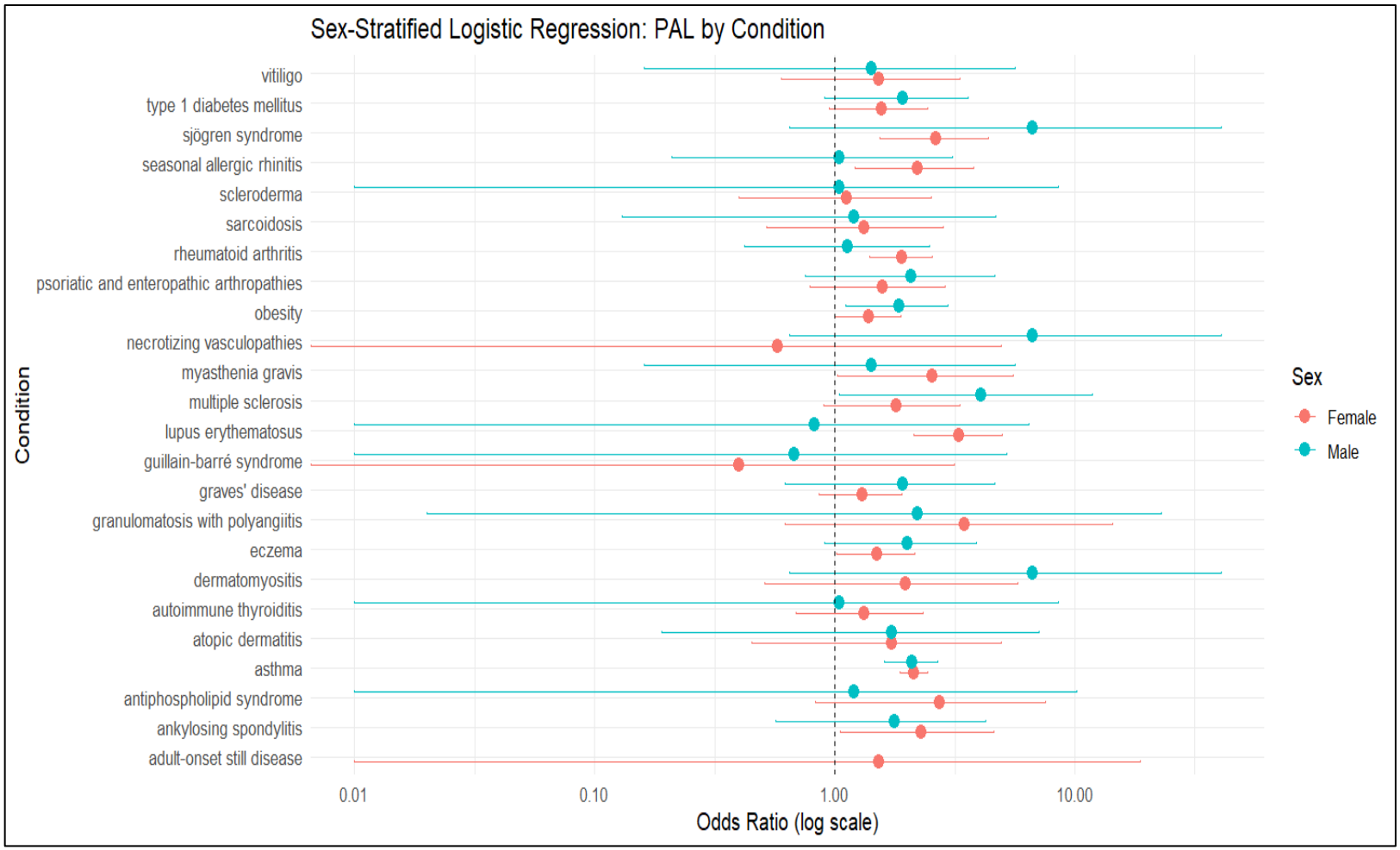


Figure 6: Association between Penicillin Allergy Label (PAL) Presence and Pre-Defined Conditions, by Sex Assigned at Birth



Tables

Table 1: Descriptions of the Study Settings, Population, and Inclusion Criteria

Author	Year	Setting	Sites	Country	Population	Sample Size of Low-Risk Participants	Inclusion criteria	Exclusion criteria	DD	OC
Randomized Controlled Trials										
Mustafa	2019	Primary care centre	1	United States	Patients ≥ 5 years	159	5 to 17 years with a history of cutaneous-only reaction to PCN >1 year ago; 18 years and older with a history of cutaneous-only reaction >10 years ago.	Pregnancy; severe cutaneous non-IgE-mediated adverse drug reaction; or a serum sickness-like reaction	☒	☑
Copaescu	2023	Outpatient clinic	6	United States, Canada, Australia	Outpatient >18 years	377	Referred to an allergy clinic with a calculated PEN-FAST score of <3	< 18 years; PEN-FAST score ≥3; pregnancy; illness that increases risk associated with participation; type A adverse drug reaction; anaphylaxis; idiopathic urticaria; macrocytosis; serum sickness; blistering skin eruption; acute interstitial nephritis; allergy history not confirmed; concurrent antihistamine therapy; more than stress dose steroids; reaction is an adverse effect.	☒	☑
Quasi-Experimental Studies										
Tucker	2017	Outpatient clinic	1	United States	Males >18 to <25 years	328	Marine recruits	PCN-associated serious cutaneous reactions (excluding urticaria/ angioedema); hepatitis; hemolytic anemia; nephritis	☒	☑
Trubiano	2018	Outpatient clinic	3	Australia	Adult cancer patients	48	Unknown reaction >10 years before; type A adverse drug reaction; history of a benign childhood rash; non-urticarial rash; maculopapular exanthem >10 years ago.	Pregnant; cognitive impairment where a collateral history could not be obtained; drug-associated anaphylaxis or angioedema; severe cutaneous adverse reactions, history of acute kidney injury or severe liver impairment associated with antibiotic therapy; hemodynamic instability.	☒	☑
Devchand	2019	Ambulatory care hospital	1	Australia	≥ 18 years prescribed ≥ 1 antibiotic	106	Adult patients	<18 years of age; intensive care; admitted under the spinal unit; cognitive impairment; developed a PCN allergy during current admission; serious PCN allergy not amenable to testing; ongoing prophylactic antibiotics (>7 days); reviewed by ID team; known to outpatient allergy service.	☑	☑

Iammatteo	2019	Outpatient clinic	1	United States	≥7 years	155	Non-life-threatening reactions to PCN	Reactions to PCN with following features: bronchospasm or laryngeal edema requiring intubation; anaphylactic shock; severe non-IgE-mediated reactions (i.e., SJS, TENs, interstitial nephritis); pregnancy; antihistamine within 3 days of enrollment.	☒	☑
duPlessis	2019	Acute care hospital	1	New Zealand	>16 and <70 years	199	Reported PAL and admitted for 24 hours	Pregnant; <16 years and >70 years; asthma or COPD that is poorly controlled or required hospitalization within 1 year of consent or ever admitted to an ICU or FEV1 <40%; allergic reaction within 4 weeks; SJS, TEN or DRESS in relation to a b-lactam antibiotic; significant cardiovascular disease; on b-blockers and ACE inhibitors; systolic blood pressure <100 mmHg; hemodynamically unstable; admitted to the mental health unit or theatre day unit; unable to give consent.	☑	☑
Savic	2019	Acute care hospital	1	United Kingdom	>18 years; surgery patients	74	Reaction occurred >15 years ago; low risk symptoms; sufficient time for testing before operation; wants to be tested; requires PCN for surgery.	High risk symptoms (anaphylaxis, angioedema, swelling of face/body, severe blistering skin rash, wheeze, shortness of breath, collapse or dizziness, itchy rash, symptoms require hospital admission and treatment); reaction <15 years ago; no time for testing, declined; PCN not required; pregnant, breastfeeding, unstable asthma.	☒	☑
Kuruvilla	2019	Acute care hospital	1	USA	Adult outpatients treated by allergist	50	History of benign rash; somatic symptoms; another unknown history associated with their last PCN exposure if it occurred >12 months ago. Patients with only GI upset or who received PCN since the index reaction, were DD.	Reaction within the past 12 months; history of PCN associated blistering rash; hemolytic anemia; organ involvement.	☑	☑
Ramsey	2020	Acute care hospital	1	United States	Inpatients ≥18 years receiving antibiotic	48	Identified as appropriate using a published PCN allergy history algorithm.	Severe cutaneous reaction; empiric or targeted therapy for resistant bacterial organism; antibiotic regimen recommended by ID; inability to provide informed consent; pregnancy.	☒	☑

Stevenson	2020	Outpatient clinic	7	Australia	≥ 16 years at immunology clinics	112	Patients who underwent PST or OC	Severe non-IgE-mediated reactions (SCARs, serum sickness, and hypersensitivity vasculitis); incomplete testing; no history of PCN exposure; suitable for delabeling by history; testing did not adequately assess implicated PCN; cardiorespiratory comorbidities such as severe asthma, structural lung disease; ischemic heart disease, or difficult airway; pregnancy.	☒	☑
Chua	2021	Ambulatory care hospital	2	Australia	Inpatients ≥ 18 years	558	Low-risk allergy using AAAT tool; unknown reaction > 10 years ago; type A adverse drug reaction; unspecified childhood rash; localized injection site reaction; maculopapular exanthem > 10 years ago.	Moderate or severe allergy history using the AAAT tool; history of any anaphylaxis or idiopathic urticaria/ anaphylaxis; hemodynamic instability; >10 mg prednisolone or corticosteroid equivalent; or antihistamine therapy.	☑	☑
Gateman	2021	Primary care centre	1	Canada	Outpatients 18 months or older	58	Considered to be at low risk of true PCN allergy.	Received PCN without reaction; IgE mediated; severe reaction (SJS, TENS, AGEP, DRESS); clinical notes/history were incomplete.	☒	☑
Sneddon	2021	Acute care hospital	1	Scotland	Inpatients in medical wards or attending pre-operative clinics	95	Without history of Type IV hypersensitivity or Type I hypersensitivity; did not occur within last 10 years; did not required admission or urgent treatment.	Immunocompromised; medically unstable (NEWS ≥ 2); pregnant; uncontrolled asthma; ACEI or BB that cannot be withheld within 24 hrs before OC; potential Type I or IV hypersensitivity; reaction that occurred within the last 10 years, required admission or urgent treatment or a reaction that occurred within an hour of drug administration.	☒	☑
Zhang	2021	Outpatient clinic	1	Canada	Pregnant women less than 36 weeks' gestation	42	Pregnant women less than 36 weeks' gestation; registered for delivery at BC Women's Hospital (including home births); reported PCN allergy	Documented history of a PCN-associated severe cutaneous adverse reaction; anaphylaxis within 1 month.	☑	☑
Song	2021	Community hospital	1	United States	≥18 years	12	Patients admitted to medical/surgical units or three labour/delivery and high-risk pregnancy units during 3-month pilot.	Patients declining interviews; unable to be interviewed.	☑	☒

Ham	2021	Acute care hospital	1	USA	≥18 years inpatients evaluated by the pharmacist	50	Active infections whose antibiotics would change based on testing received highest priority; not undergoing treatment received lower priority.	Pregnant patients excluded; critically ill or receiving medications that would interfere with testing were evaluated only when referred.	☑	☑
Steenvoorden	2021	Acute care hospital	1	Norway	All patients admitted to the department of internal medicine	57	History of benign rash; symptoms unlikely to be of allergic etiology (headache, mild GI symptoms); no recollection of reaction.	Prior PCN elicited IgE medicated reactions; severe, non-IgE mediated reactions; ongoing critical illness; recent reaction to PCN (<1 year ago); severe anaphylaxis of any cause during the last 4 weeks before inclusion.	☒	☑
Fransson	2022	Outpatient clinic	1	Denmark	Adult patients	202	Suspected allergy to penicillin G, penicillin V, aminopenicillins, or unknown PCN; low-risk history of PCN allergy	High risk history; severe comorbidities such as COPD, asthma, ischemic heart disease and heart failure; pregnancy or breastfeeding; specific IgE levels for PCNs above 0.35 kUA/L	☒	☑
Livirya	2022	Acute care hospital	1	New Zealand	Inpatients at a general internal medicine department	162	Limited cutaneous reaction (including rash and hives); unknown symptoms occurring ≥6 months ago and ≥1 h after drug administration; suitable for an oral challenge; history of a mild ADR such as GI upset; received PCN antibiotics after index reaction.	History of a severe cutaneous reaction such as SJS, TENS, DRESS, drug-induced exfoliative dermatitis or a severe blistering rash; interstitial nephritis, vasculitis or haemolytic anaemia; or anaphylaxis or recent (<6 months ago) angioedema, cutaneous or respiratory symptoms; actively dying; frail; hemodynamically unstable; immunosuppressed (prednisone >20 mg daily or equivalent); pregnant.	☑	☑
Koo	2022	Acute care hospital	1	United States	Admitted to medical intensive care unit	240	Hemodynamically stable; not pregnant; cognitively capable of providing a history; PAL low risk.	Patients with moderate to high-risk allergy history excluded but no distinct exclusion criteria described.	☒	☑
Fanizza	2022	Ambulatory care hospital	1	United States	Adults referred by prescriber who completed PCN allergy testing	27	Adults at outpatient clinic	Immediate type I hypersensitivity reaction within the past 5 years; severe skin reaction such as SJS or TENS after receiving any PCN; using antihistamines (instructed to hold the medication for 3-5 days before their appointment to minimize the risk of masking an allergic reaction).	☒	☑
Trubiano	2022	Acute care hospital	1	Australia	All patients on admission with a low-risk PCN allergy	478	Unknown reaction >10 years before; type A adverse drug reaction; history of a benign childhood rash, non-urticarial rash, or maculopapular exanthem > 10 years ago.	Pregnant; cognitive impairment where a collateral history could not be obtained; drug-associated anaphylaxis or angioedema; severe cutaneous adverse reactions, history of acute kidney injury or severe liver impairment associated with antibiotic therapy; hemodynamic instability.	☒	☑

Mak	2022	Outpatient clinic	1	Canada	Pregnant women in third trimester	216	Pregnant woman between 28-36 weeks' gestation that had a history of PCN allergy and PEN-FAST score of 0	Patients with PEN-FAST score of 1 or greater were categorized into moderate and high risk	☑	☑
Alnaes	2023	Acute care hospital	1	Norway	≥18 years admitted to ID ward or referred to allergy clinic.	74	Self-reported PCN allergy; PCN allergy registered in medical record.	Critically ill; respiratory and/or hemodynamic instability	☒	☑
Rozario	2023	Community hospital	2	United States	Patients for whom an amoxicillin challenge order-set was used	81	Delabeled by hospitalists and non-allergy specialists	Delabeled via allergy/immunology consultation.	☒	☑
Wade	2023	Acute care hospital	1	United Kingdom	Adult patients seen at the pre-admit surgical clinic	10	Adult patients (≥18 years of age)	Not specified	☑	☒
Stollings	2023	Acute care hospital	1	United States	All patients admitted to MICU with PAL and COVID 19	24	Hemodynamically stable; not receiving non-invasive or invasive mechanical ventilation; not pregnant, not a prisoner; could provide a history of their index reaction.	Hemodynamically unstable; receiving non-invasive or invasive mechanical ventilation; pregnant; prisoner; could not provide a history of their index reaction.	☒	☑

Legend:
AAAT: Antibiotic Allergy Assessment Tool; ACEI: Angiotensin Converting Enzyme Inhibitor; ADR: Adverse Drug Reaction; AGEP: Acute Generalized Exanthematous Pustulosis; BB: Beta-Blocker; ICU: Intensive Care Unit; COPD: Chronic Obstructive Pulmonary Disease; DD: Direct Delabel; DRESS: Drug rash with eosinophilia and systemic symptoms; FEV: Forced Expiratory Volume; GI: Gastrointestinal; ID: Infectious Diseases; MICU: Medical Intensive Care Unit; NEWS: National Early Warning Score; OC: Oral Challenge; PAL: Penicillin Allergy Label; PCN: Penicillin; PST: Penicillin Skin Testing; SCAR: Severe Cutaneous Adverse Reactions; SJS: Stevens Johnson Syndrome; TENs: Toxic Epidermal Necrolysis.

Table 2: Baseline Self-Reported or Reported Reactions to Penicillins

First Author	Year	Childhood exanthem	Immediate diffuse rash	Diffuse rash <10 years	Diffuse rash >/= 10 years	Blistering or desquamating rash	Angioedema	Swelling	Urticaria	Laryngeal involvement	Respiratory compromise	Fever	Anaphylaxis	Hematologic	Unknown reaction <10 years	Unknown reaction >10 years	Liver or renal injury (severe)	Liver or renal injury (mild)	Gastrointestinal symptoms	Neurologic or CNS symptoms (severe)	Neurologic or CNS symptoms (mild)	Pruritis	Other
Chau, K	2021	9%	11%	9%	22%	4%	12%	7%	9%	4%	6%	1%	7%	0%	1%	9%	1%	1%	13%	1%	2%	-	10%
Duplessis, T	2019	28%	-	-	-	-	10%	3%	-	-	-	-	-	-	-	-	3%	-	33%	12%	-	-	12%
Fanizza FA	2022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	36%	-	-	-	-	-	-	39%
Gateman, DP	2021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	9%
Ham, Y	2021	-	50%	-	-	-	6%	-	28%	-	22%	-	-	-	-	-	-	-	6%	-	-	-	22%
Iammatteo, M	2019	-	5%	-	24%	-	4%	-	40%	2%	-	-	-	-	-	15%	-	-	1%	-	-	3%	7%
Kuruvilla, M	2019	-	-	-	-	4%	-	-	38%	-	-	-	38%	-	-	-	-	-	4%	-	-	38%	-
Livirya, S	2022	31%	-	-	-	7%	5%	-	-	-	4%	-	11%	-	-	24%	-	-	17%	-	-	-	4%
Mak, R	2022	-	-	-	49%	-	9%	-	34%	-	5%	-	-	-	15%	15%	-	-	-	-	-	-	-
Mustafa, S	2019	-	-	-	47%	-	-	-	30%	-	-	-	-	-	-	6%	-	-	-	-	-	-	-
Ramsey, A	2020	-	-	-	46%	-	-	-	42%	-	-	-	-	-	-	8%	-	-	-	-	-	4%	-
Rozario, C	2023	-	-	38%	-	-	-	4%	26%	-	-	-	1%	-	19%	-	-	-	-	-	-	-	7%
Sneddon, J	2021	-	-	-	37%	-	7%	-	-	-	-	-	-	-	-	38%	-	-	6%	4%	-	-	8%
Steenvoorden, L	2021	-	-	-	-	-	26%	-	28%	-	23%	-	20%	-	-	-	-	-	-	-	-	-	-
Stollings, J	2023	-	-	-	-	-	-	-	-	-	-	-	22%	-	-	-	-	-	-	-	-	-	0%
Trubiano, JA	2018	26%	-	-	30%	-	-	-	-	-	-	-	-	-	37%	-	-	-	-	-	-	-	9%
Tucker	2017	76%	-	-	-	-	-	-	-	-	-	-	-	-	-	20%	-	-	1%	-	-	-	2%
Zhang, BY	2021	-	-	-	68%	-	-	-	11%	-	-	-	-	-	-	25%	-	-	-	-	-	-	-

Legend: Dash (-) indicates that data is not reported

Table 3: Protocol Descriptions and Reported Reactions

First author	Year	Index Reactions Described	Reactions to Oral Challenge n=, (%)	Drug(s) Used	Dose	Frequency	Provider	Comments
Alnaes	2023	No	1 (1%)	Index penicillin (if known) Amoxicillin (if index not known)	NR 500 mg	ONCE	NR	Non-severe rash
Chau	2021	Yes	9 (5%)	Penicillin Amoxicillin Amoxicillin	250 mg 250 mg 500 mg	ONCE ONCE BID for 5 days	Nurse	6 positive oral challenges and 3 non-immune-mediated reactions
Copaescu	2023	No	1 (1%)	Penicillin VK Amoxicillin Flucloxacillin	Variable	NR	Other	1 immune mediated reaction in both arms
Devchand	2019	No	NR	NR	NR	NR	Nurse	No follow up once delabeling completed
duPlessis	2019	Yes	3 (9%)	Amoxicillin	Graded oral challenge suspended in yogurt given 30 min apart until 1000 mg TID	24 hours, if continued use not required	Pharmacist	Only nausea, vomiting, or headache were reported reactions
Fanizza	2022	Yes	0 (0%)	Amoxicillin	250 mg	ONCE	Pharmacist	No reactions were described
Fransson	2022	No	20 (10%)	Amoxicillin	500 mg	ONCE or Twice daily	Patient self-completed	19 cutaneous symptoms, 1 hyperventilation 13 of 19 cutaneous reactions were experienced 3 days after oral challenge

Gateman	2021	Yes	3 (3%)	Amoxicillin	Graded	ONCE	Primary care provider	3 pediatric patients had a reaction No adult patients had a reaction
Ham	2021	Yes	2 (7%)	Amoxicillin	250 mg	ONCE	Pharmacist	Two patients retained their allergy label due to mild reactions in the two-step challenge
Iammatteo	2019	Yes	19 (12%)	Amoxicillin	80 mg and 500 mg	80 mg ONCE, observe for 30 min then 500 mg ONCE	Other	4 described as allergic and 15 non-allergic reactions
Koo	2022	No	NR	Amoxicillin	250 mg	ONCE	Other	NR
Kuruvilla	2019	Yes	3 (15%)	Amoxicillin	500 mg	ONCE	Allergist/ immunologist	3 reactions reported: chest tightness, pruritis, and dizziness
Livirya	2022	Yes	4 (10%)	Amoxicillin	250 mg	ONCE	Nurse	Description of reactions not reported Relabeling on follow-up
Mak	2022	Yes	4 (2%)	Amoxicillin	500 mg	ONCE	Other	No immediate hypersensitivity, 4 delayed cutaneous reactions, 1 vomiting (unrelated to challenge)
Mustafa	2019	Yes	3 (4%)	Amoxicillin	400 mg	ONCE	Allergist/ immunologist	No reactions in penicillin skin test arm 3 cutaneous reactions (treated with antihistamines) in oral challenge arm
Ramsey	2020	Yes	3 (6%)	Amoxicillin	Graded or 500 mg	30-minute intervals or ONCE	Nurse	1 rash with amoxicillin/clavulanate on day 17 of therapy 1 facial swelling and nausea/vomiting with amoxicillin/clavulanate on the day after challenge 1 from the skin testing group experienced a rash with cefazolin on day 17 of therapy

Rozario	2023	Yes	2 (2%)	Amoxicillin	250 mg	ONCE	Other	Of the 79 patients who were delabeled, allergy label was only removed from EMR for 64 (81%) 2 cases of delayed reactions
Savic	2019	No	1 (2%)	Amoxicillin	Incremental dose increase	ONCE	Nurse	1 patient with index reaction of widespread urticaria (not initially disclosed to research team) developed urticaria in hands after the second dose and stopped taking the amoxicillin
Sneddon	2021	Yes	1 (1%)	Amoxicillin Flucloxacillin	500 mg	ONCE	Other	1 patient did not have a documented success or failure and was therefore deemed non-successful
Steenvoorden	2021	Yes	2 (4%)	Amoxicillin	75 mg 250 mg	ONCE	Other	1 admitted patient had worsening of pre-existing bronchial obstruction symptoms, resolved with ipratropium bromide-salbutamol inhalation, was not delabeled 1 patient reported a mild maculopapular rash 2 days after oral challenge, not treated and was delabeled
Stevenson	2020	No	6 (4%)	Amoxicillin	NR	NR	Other	Direct challenge was performed for both low and moderate risk cases, but specifics not described in text
Stollings	2023	Yes	NR	Amoxicillin	250 mg	ONCE	Pharmacist	NR
Trubiano	2022	No	20 (4%)	Penicillin VK Amoxicillin	250 mg	ONCE	Nurse	10 immune mediated (9 delayed rash, 1 immediate rash, 1 decreased consciousness, 1 self-resolving throat tightness, 1 fever, and 1 unknown; none required epinephrine) and 10 non-immune mediated
Trubiano	2018	Yes	0 (0%)	Penicillin VK Amoxicillin Amoxicillin	250 mg	ONCE ONCE BID	Nurse	No reactions reported
Tucker	2017	Yes	5 (2%)	Amoxicillin	250 mg	ONCE	Not defined	NR
Zhang	2021	Yes	NR	Amoxicillin	NR	NR	Allergist/ immunologist	No reactions reported

Legend- BID: twice daily; EMR: electronic medical record; NR: not reported; TID: three times daily

Table 4: Demographics and Allergy Labels

Variable	Category	Overall n (%)	Female n (%)	Male n (%)
Population	–	29, 645	17,707 (59.7)	11,938 (40.3)
Mean Age in years (SD)	–	54.7 (SD: 19.8)	53.9 (SD: 20.1)	55.8 (SD: 19.3)
Medication Allergy Labels	Any medication allergy	7,245 (24.4)	5,328 (30.1)	1,914 (16.0)
	1 medication allergy	(62.8)	(59.4)	(72.3)
	2 medication allergies	(20.4)	(21.4)	(17.8)
	≥3 medication allergies	(16.7)	(19.2)	(10)
Beta-lactam Allergy Label (BLA)	Any BLA	3,026 (10.2)	2,247 (12.7)	779 (6.6)
	Penicillin-class	(92)	–	–
	Cephalosporin-class	(12)	–	–
	Carbapenem-class	(<1%)	–	–
Penicillin Allergy Label (PAL)	PAL	2,777 (9.4)	2,057 (11.6)	720 (6.0)
	Low-risk PAL	2,518 (91.7)	1,866 (10.5)	652 (5.5)
	High-risk PAL	259 (9.3)	191 (1.1)	68 (0.6)
PAL, mean age in years (SD)	–	57.7 (19.4)	57.7 (19.4)	57.7 (19.3)

Table 5: Multivariable Logistic Regression Model

Variable	With PAL	Total	OR (CI)	P value
Sex				
Male Female	720 2,057	11,938 17,707	Ref 1.47 (1.34–1.62)	 <0.001
Condition Categories (no Ref.)				
Atopic Conditions Autoimmune Inflammatory conditions Metabolic conditions (obesity)	428 238 63	2,507 1,538 469	1.46 (1.29–1.66) 1.07 (0.91–1.26) 1.00 (0.73–1.34)	<0.001 =0.408 =0.998
Age Group				
<65 years 65–80 years >80 years	1,635 742 400	19,259 6,844 3,542	Ref 1.08 (0.98–1.20) 1.16 (1.02–1.32)	 =0.132 <0.05
Medication Allergy Count				
0-1 2 ≥3	1,577 620 580	26,986 1,478 1,181	ref 10.44 (9.28–11.74) 13.33 (11.72–15.16)	 <0.001 <0.001

Legend: 95% Confidence Interval (95% CI); Reference Category (Ref); Not Applicable (NA); Odds Ratio (OR); PAL (Penicillin Allergy Label)

Table 6: Intersectional and Sociodemographic Variables

Variable	Category	Overall n (%)
Education Level	Not reported	29,645 (100)
Ethnic Group	White – North American	416 (1.4)
	White – European	328 (1.1)
	Asian – South	61 (0.2)
	Asian – East	52 (0.2)
	Other	1,460 (4.9)
	Not reported	27,328 (92.2)
Gender Identity	Other	106 (0.4)
	Not reported	29,539 (99.6)
Language	English	8,463 (28.5)
	Portuguese	219 (0.7)
	Spanish	103 (0.3)
	Chinese (Cantonese)	78 (0.3)
	Other	795 (2.7)
	Not reported	19,987 (67.4)
Religion	Roman Catholic	415 (1.4)
	Jewish	193 (0.6)
	Christian Other	170 (0.6)
	Anglican	149 (0.5)
	Protestant	91 (0.3)
	Muslim	90 (0.3)
	Spiritual	69 (0.2)
	Non-Denominational	50 (0.2)
	Other	2,006 (6.7)
	Not reported	26,462 (89.1)

*Small sample sizes are combined into an “other” category

Table 7: Demographic summary by penicillin allergy label (PAL) presence and by sex for patients seen in an urgent medicine clinic, 2015-2024.

	Female (N=17, 707)		Male (N=11, 938)		ASD (PAL Status)
	PAL Present (n=2057 [12%])	PAL Absent (n=15,650 [88%])	PAL Present (n=720 [6%])	PAL Absent (n=11,218 [94%])	
Population					
Age, mean (SD)	57.7 (19.4)	53.5 (20.1)	57.7 (19.3)	55.7 (19.3)	0.17
Medication Allergy Label Frequency, n (%)					
0-1	931 (45.3%)	14,077 (89.9%)	459 (63.8%)	10,805 (96.3%)	1.07
2	528 (25.7%)	930 (5.9%)	174 (24.2%)	272 (2.4%)	0.61
3 or more	598 (29.1%)	643 (4.1%)	87 (12.1%)	141 (1.3%)	0.66
Common Medical Conditions, n (%)					
Coronary artery disease	811 (39.4%)	4,567 (29.2%)	315 (43.8%)	4,042 (36.0%)	0.18
Hypertension	636 (30.9%)	3,805 (24.3%)	255 (35.4%)	3,364 (30.0%)	0.12
Diabetes	298 (14.5%)	1,755 (11.2%)	150 (20.8%)	1,882 (16.8%)	0.07
Gastroesophageal reflux disease	309 (15.0%)	1,441 (9.2%)	78 (10.8%)	791 (7.1%)	0.18
Depression	282 (13.7%)	1,595 (10.2%)	64 (8.9%)	643 (5.7%)	0.14
Arthritis	279 (13.6%)	1,362 (8.7%)	42 (5.8%)	527 (4.7%)	0.16
Asthma	316 (15.4%)	1,231 (7.9%)	72 (10.0%)	575 (5.1%)	0.24
Anxiety	234 (11.4%)	1,352 (8.6%)	44 (6.1%)	524 (4.7%)	0.11
Hypothyroidism	271 (13.2%)	1,378 (8.8%)	40 (5.6%)	390 (3.5%)	0.16
Obstructive sleep apnea	145 (7.0%)	711 (4.5%)	71 (9.9%)	817 (7.3%)	0.08
Conditions Associated with PAL Presence, n (%)					
Atopic conditions	350 (17.0%)	1, 416 (9.0%)	78 (10.8%)	633 (5.9%)	0.24
Autoimmune inflammatory conditions	205 (10.0%)	932 (6.0%)	33 (4.6%)	368 (3.3%)	0.15
Metabolic condition (obesity)	45 (2.2%)	250 (1.6%)	18 (2.5%)	156 (1.4%)	0.06
Medical Conditions Associated with Increased Burden of Infection (not found in Common Medical Conditions), n (%) *					
Cancer	67 (3.0%)	330 (2.1%)	NR	17 (0.2%)	0.08
Chronic obstructive pulmonary disease	94 (4.6%)	295 (1.2%)	41 (5.7%)	448 (4.0%)	0.11

Chronic kidney disease	86 (4.2%)	413 (2.6%)	49 (6.8%)	556 (5.0%)	0.06
Cirrhosis	17 (0.8%)	76 (0.5%)	12 (1.7%)	142 (1.3%)	0.02
Heart failure	70 (3.4%)	366 (2.3%)	30 (4.2%)	367 (3.3%)	0.05
Seen for an Infectious Disease-Related Encounter, n (%)					
No	2,027 (98.5%)	15,480 (98.9%)	706 (98.1%)	11,038 (98.4%)	0.02
Yes	30 (1.5%)	170 (1.1%)	14 (1.9%)	180 (1.6%)	0.02

Legend: NR-Not Reported; ASD- Absolute Standardized Difference

Table 8: Association between PAL status, sex, and antibiotic utilization, base and adjusted regression models

Exposure Variables†	**Number of Patients Using an Antibiotic**	**Base Model Odds Ratio (95% CI)**	**Adjusted model‡ Odds Ratio (95% CI)**
PAL (Present)	343	1.34 (1.16 – 1.56)	1.25 (1.09 – 1.43)
Sex (Female)	1583	0.72 (0.67-0.78)	0.73 (0.67 – 0.79)

†PAL*SEX removed from model due to non-significant interaction (p-value = 0.27)
‡Covariates included PAL, sex, age, allergy label frequency, presence of atopic conditions, autoimmune inflammatory conditions, autoimmune conditions, and chronic obstructive pulmonary disease.

Table 9: Antibiotic class prescribing reported by sex for the sub-cohort of patients who received an antibiotic at first encounter

Antibiotic Class	Female (N= 1,543)		Male (N= 1,365)	
	PAL Present (n=226 [15%])	PAL Absent (n=1,317 [85%])	PAL Present (n= 117 [9%])	PAL Absent (N=1,248 [91%])
Aminoglycosides	NR	9 (0.7%)	NR	7 (0.5%)
Carbapenems	NR	19 (1.4%)	NR	21 (1.7%)
Cephalosporins	48 (21.2%)	351 (26.7%)	33 (28.2%)	357 (28.6%)
Fluoroquinolones	80 (35.4%)	224 (17.0%)	35 (30.0%)	247 (19.8%)
Folate synthesis inhibitors	14 (6.2%)	86 (6.5%)	13 (11.1%)	111 (8.9%)
Lincosamides or glycopeptides	23 (10.1%)	49 (3.7%)	12 (10.3%)	45 (3.6%)
Macrolides	30 (13.3%)	102 (7.7%)	10 (8.5%)	97 (7.8%)
Other	33 (14.6%)	183 (13.9%)	6 (5.1%)	107 (8.6%)
Penicillins	18 (8.0%)	443 (33.6%)	15 (12.8%)	444 (35.6%)
Tetracyclines	20 (8.8%)	89 (6.8%)	12 (10.3%)	67 (5.4%)
Topical Agents	10 (4.4%)	86 (6.5%)	8 (6.8%)	69 (5.5%)

Legend: NR-Not Reported

Table 10: Associations of PAL status and sex with antibiotic class utilization among the sub-cohort of patients prescribed an antibiotic at first encounter

	PAL		Female Sex		Base Interaction Model	Adjusted Interaction Model
Antibiotic class	**†Base model OR (95% CI)**	**‡Adjusted model OR (95% CI)**	**†Base model OR (95% CI)**	**‡Adjusted model OR (95% CI)**	**p value for PAL*sex**	**p value for PAL*sex**
Penicillins	0.56 (0.31-0.88)	0.33 (0.23-0.48)	0.72 (0.63-0.83)	0.73 (0.63-0.83)	0.09	0.06
Cephalosporins	1.41 (0.95-2.10)	1.08 (0.82-1.43)	0.67 (0.57-0.79)	0.66 (0.56-0.77)	0.30	0.27
Carbapenems	2.23 (0.59-8.40)	1.96 (0.80-4.79)	0.51 (0.25-1.06)	0.57 (0.30-1.08)	0.73	0.77
Macrolides	3.03 (1.56-5.89)	2.94 (1.96-4.40)	0.94 (0.66-1.34)	0.90 (0.72-1.36)	0.92	0.97
Fluoroquinolones	2.17 (1.46-3.23)	2.54 (1.96-3.28)	0.63 (0.51-0.77)	0.69 (0.57-0.82)	0.29	0.29
Tetracyclines	3.73 (1.95-7.13)	1.66 (1.02-2.69)	0.95 (0.66-1.38)	0.74 (0.53-1.05)	0.11	0.06
Topical Agents	2.57 (1.04-6.35)	1.07 (0.57-2.01)	1.08 (0.70-1.67)	0.95 (0.63-1.43)	0.28	0.17
Aminoglycosides	2.22 (0.11-43.17)	1.62 (0.46-5.69)	1.13 (0.29-4.30)	1.37 (0.43-4.32)	0.99	0.99
Lincosamides and Glycopeptides	5.80 (2.85-11.83)	4.50 (2.69-7.54)	0.77 (0.46-1.28)	0.67 (0.44-1.04)	0.51	0.56
Folate Synthesis Inhibitors	1.31 (0.59-2.93)	0.91 (0.51-1.61)	0.58 (0.41-0.81)	0.53 (0.38-0.73)	0.86	0.63
Other Antibiotic Classes	1.12 (0.38-3.34)	1.24 (0.77-1.99)	1.73 (1.23-2.42)	1.82 (1.32-2.52)	0.64	0.67

Legend: CI- Confidence Interval; OR- Odds Ratio; PAL- Penicillin Allergy Label
Sample sizes for each antibiotic class can be found in Table 3
Base interaction model includes PAL, sex, PAL*sex
Adjusted interaction model PAL, sex, PAL*sex, age, allergy label frequency, presence of atopic conditions, autoimmune inflammatory conditions, autoimmune conditions, and chronic obstructive pulmonary disease.

†Covariates include PAL and sex
‡Covariates included PAL, sex, age, allergy label frequency, presence of atopic conditions, autoimmune inflammatory conditions, autoimmune conditions, and chronic obstructive pulmonary disease.

Appendices

Appendix A: Co-Designed Systematic Review and Meta-Analysis Protocol

Background

Antibiotics in the β-lactam family (penicillin, amoxicillin, etc.) are often first-line therapeutic options for many infectious diseases, including skin and soft tissue infections, diabetic foot infections, (5,87,88) respiratory tract infections, bloodstream infections, and other life-threatening conditions (6,7). However, approximately 10% of the general population carries the label of a penicillin allergy (7) and up to 15% of hospitalized patients are reported to have a documented penicillin allergy (21).

Applying the label of "penicillin allergy" without sufficient investigation and verification has led to substantial shifts away from the use of the most studied and effective therapeutic regimens towards the use of alternative antimicrobial agents. Compared to β-lactams, in which penicillins are classified, these agents are associated with higher rates of hospital acquired infections such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridioides difficile*, and vancomycin resistant *Enterococcus* (VRE) infections (7). Further, the use of second-line or broad-spectrum non-β lactam therapies has been associated with increased hospital length of stay, increased cost of hospitalization, decreased likelihood of infection resolution, infection recurrence, and increased risk of drug toxicity (7).

Following assessment of a purported penicillin allergy, 90% to 95% of individuals have been found to tolerate penicillins (89). Penicillin allergy delabeling can be carried out through skin testing, serum specific immunoglobulin E testing for β-lactams, oral challenge and delabeling on clinical history (7). Penicillin skin testing (PST) has historically been the gold standard method of penicillin allergy assessment with a positive predictive value of between 50% to 75%, (7) althought interpretation depends on the true prevalence of penicillin allergy in a population. A systematic review and meta-analysis of the diagnostic accuracy of penicillin allergy testing using a variety of modalities was conducted, with data collected from studies involving adult and pediatric cases (62); for skin tests, sensitivity was low (30.7%, 95%CI of 18.9% to 45.9%) and specificity high(96.8%, 95%CI of 94.2% to 98.3%). Considering the heterogeneity of results for sensitivity, specificity, and predictive value, PST may be a poor screening tool in patients with low-risk penicillin allergies. Given these limitations, oral provocation challenge has become an accepted gold standard method to address penicillin allergy labels in low-risk individuals (7,89,90).

For this review, low risk reactions include remote mild cutaneous reactions, reactions that are often considered as side effects (e.g., diarrhea or nausea) and reactions of unknown history with tolerance to a within class β-lactam in the past (89,90). It is important to note that studies vary by the categorization and definition of "Low-Risk". The importance of this variability became clear during an Ontario Pharmacy

Evidence Network (OPEN) Citizen's Council discussion where feedback from the public was sought on questions related to our study design with a focus on barriers and facilitators for co-design of our protocol. The participants expressed the importance of clear definitions that included patient friendly language for words such as "allergy", "intolerance", "high-risk" and "low-risk" allergies. Based on this feedback, our team will focus on obtaining a list of inclusion criteria from published literature that report penicillin allergy delabeling in "low-risk" populations to determine the most common components of a "low-risk" definition for both direct delabeling and oral challenge.

Another important consideration is the association between penicillin allergy prevalence and outcomes between male and female individuals as well as the associated gender-related variables that may impact these factors, such as healthcare seeking behaviours. Historically, female sex has been associated with higher rates of adverse drug reactions (ADRs) (91) and the reported prevalence of penicillin allergy may be higher in female adult patients (22,23,73). However, it is not clear whether the association is with sex or gender or a combination thereof. Biologic sex has been shown to influence pharmacokinetics, pharmacodynamic processes, and response to drug activity (70). There is also speculation that the female propensity to drug allergy may be related to a multitude of factors including social constructs such as different utilizations of healthcare (78,81). Therefore, there may be both biologic and gender-related factors that may contribute to varied reporting of penicillin allergies and patient outcomes by sex.

Therefore, the purpose of this systematic review and meta-analysis will include identifying, assessing the quality of, and synthesizing results from studies reporting on the effectiveness and safety of interventions designed to delabel penicillin allergies in the adult population by history, questionnaire, or oral challenge in comparison to no intervention, penicillin allergy skin testing or other interventions. Sex and Gender-Based Analysis Plus (SGBA+) information will be extracted, where available to understand sex and gender differences in allergy reporting and outcomes associated with delabeling interventions in the published literature focusing on low-risk allergies.

Methods and Design

The Cochrane Handbook for Systematic Reviews of Interventions (92) and the Centre for Review and Dissemination's Guidance for Undertaking Reviews in Health Care (93) will be used as frameworks for conducting this systematic review and meta-analysis. The PRISMA-P 2015 checklist (201) will be used to include recommended items for this systematic review protocol. COVIDENCE software will be used for study screening. Microsoft Excel will be used for data extraction. The PRISMA-P 2015 checklist will be

used to display the steps of the systematic review (Appendix A). The study is registered with PROSPERO (#336457).

The research questions we aim to answer are: 1) What is the proportion of successfully delabeled penicillin allergies in low-risk patients with a penicillin allergy when delabeling of the allergy is done by history, structured questionnaire, or oral challenge in both in-patient and outpatient settings? and 2) Among published studies, are there sex or gender differences in the population included or outcomes of the interventions?

The primary objective of this systematic review and meta-analysis will be to quantify the percentage of successfully delabeled penicillin allergies in the studied population by proposed intervention, where successful delabeling is defined as an allergy label being removed from a patient's medical profile after successful implementation of an intervention. The secondary objectives will include: 1) determining differences between prescribed therapies in intervention and control arms, such as antibiotics used (targeted or broad spectrum, number of antibiotics) , 2) duration of antibiotic therapy in intervention and control arms, 3) secondary infections in intervention and control arms, 4) treatment success, reinfection, or re-admission in intervention and control arms, 5) cost of therapy or cost savings in intervention and control arms, and 6) prescribing practice changes over time in intervention arm. Sex and Gender-Based Analysis Plus (SGBA+) information will be extracted, where available to understand sex and gender differences in allergy reporting and outcomes associated with delabeling interventions.

Eligibility Criteria

Inclusion

- Studies involving patients with reported penicillin allergies
- Studies that include direct delabeling, delabeling using patient history or oral challenge
- Randomized controlled trials, non-randomized studies including quasi-experimental studies (e.g. interrupted time series, before and after analyses), cohort studies, case-control studies, cross-sectional studies
- Primary outcome must include penicillin allergy delabeling
- Adult (18 years of age or older) population
- Studies from all countries will be considered

Exclusion

- Non-English language text (due to lack of funding for translator)
- Studies focusing solely on pediatric populations (<18 years of age) or where data cannot be separated for pediatric and adult individuals

- Animal research and in-vitro studies
- Case reports, case series, editorials, opinions, and commentaries
- Delabeling of non-penicillin β-lactams only
- Studies where all participants underwent penicillin skin testing as a first step

An integrated knowledge translation co-design strategy (94) with involvement of key stakeholders such as pharmacists, physicians, nurses, a public citizens' council and administrative as well as leadership personnel will be implemented to optimize the study protocol design. The key stakeholders are involved in the 3 phases of this knowledge synthesis project: 1) protocol design; 2) critical review of the manuscript; and 3) dissemination of the findings to local practice.

Search Strategy

Prior to embarking on this knowledge synthesis, a search of different electronic databases was conducted based on the Centre for Reviews and Dissemination guidance (93). This search was performed on February 23, 2022, to ensure that duplication of already existing work is not conducted. The following databases were searched from inception and without limiters for language: 1) The Database of Abstracts of Reviews of Effects (DARE), The Cochrane Database of Systematic Reviews (CDSR), and the International Prospective Register of Systematic Reviews (PROSPERO). One of the studies from the PROSPERO database (202) contained a systematic review protocol focusing on delabeling penicillin allergy by history and/or oral challenge as a secondary outcome; however, the authors of that protocolr aim to evalulate the existing published evidence on the effectiveness of penicillin allergy testing and delabeling, with a focus on oral challenge alone without integrating a sex or gender perspective. Based on the search of existing or ongoing reviews from the DARE, CDSR and PROSPERO databases, we were able to determine that a knowledge synthesis on our study question of interest was reasonable to conduct.

Literature Search

A systematic search of the literature was conducted in March of 2022 by a research librarian (BMM) at the University of Waterloo. The search included electronic databases, namely PubMed, the Database of Abstracts of Reviews and Effects (DARE), Clinicaltrials.Gov, the Cochrane database of systematic reviews (CDSR) and Library, International Pharmacy Abstracts, MedRXiv, Ovid MEDLINE, and Ovid EMBASE. The search strategy was developed using a combination of keywords: *penicillin*, or *β-lactams*, and *allergy*, *and direct challenge* and *de-labelling* within an adult population. The keyword strategy was then combined with PubMed's clinical queries filters, and the full search strategy for PubMed is shown in Appendix B. Any additional database-specific translations of the search strategy are available upon request. There were no language or date filters applied to the search strategy. In addition, to ensure

coverage of related research, all the references from selected publications were reviewed and all relevant articles were included. From March 17, 2020, to April of 2023, the research librarian continued to monitor the results feeds of active database search strategies and alerted the researchers of any additional results. The search update was run again in full on October 2, 2023. The initial literature search will be broad, with a focus on title and abstract screening of the retrieved studies conducted independently by two reviewers after calibration of the first 20 articles screened. The second screen of full-text articles will be performed independently by two reviewers and the Cohen's Kappa for inter-rater reliability will be reported. Any conflicts between the two reviewers will be resolved through discussion and agreement, or, in the case of non-resolution, by involving another reviewer to serve as an adjudicator.

Appraising Risk of Bias

The Cochrane's Risk of Bias assessment tool (97) will be used to interpret risk of bias in randomized trials and the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) (98) tool will be used as a guide for non-randomized trials and quasi-experimental studies. To reduce risk of bias in study assessment, two reviewers will independently appraise the risk of bias for each study and discuss results to resolve discrepancies. R-Studio or Microsoft Excel will be used, where applicable, to generate interpretable outputs of the assessed risk of bias. Qualitative research components will be narratively described.

Data Extraction

Data will be extracted using a Microsoft Excel template and reported at 4 levels: 1) study level, 2) patient level, 3) intervention level, and 4) outcome level (as outlined below) and subdivided by data types into the following categories, where possible: 1) descriptive, 2) dichotomous/categorical, and 3) continuous. The data extraction levels, and subdivided categories can be found in Table 1. Data available in manuscripts and supplementary material will be included; however, authors will not be contacted to obtain any further data.

Definitions provided by authors such as "low risk" penicillin allergy and those for each level and category below will be narratively described and thematically analyzed, where possible. Age will be categorized as mean, median, and range. Variables from PROGRESS elements (race/ethnicity/culture, language, occupation, gender/sex, religion, education, socioeconomic status, and social capital) will be extracted to identify factors that may impact health equity from a gender lens (76). Reporting of outcome as intention to treat, per protocol, or not specified, and sex/gender analyses, where performed, will be narratively summarized. Outcome measures associated with hypersensitivity reaction will be categorized by reaction type. Where possible, timing of reaction will be categorized as greater than 10 years ago or less

than and equal to 10 years ago where defined. If longitudinal follow-up is provided, information regarding antimicrobial use, duration, length of stay, and presence or absence of MDROs will be collected.

Initial calibration of data extraction will be performed on 5 full-text articles considered for inclusion by 2 members of the research team and conflicts will be resolved by discussion or involvement of a third reviewer. Recording of individuals performing data extraction and the date of data extraction will be maintained in COVIDENCE (95). If study outcomes differ from protocol to final report, this will be discussed narratively in the systematic review results.

Data Synthesis and Analysis

The intervention effect will be expressed numerically for each study using mean differences for continuous outcomes and relative risks or risk differences for categorical outcomes. For continuous outcomes whereby the measurement scale is not the same across studies, the standardized mean difference, or Cohen's effect, will be used. The results of single-arm quasi-experimental studies will be reported using mean change for continuous outcomes and proportions for dichotomous outcome.

A meta-analysis will be performed for the primary and secondary outcomes, stratified by intervention type (history/questionnaire, oral challenge, skin testing [reference group for pair-wise meta-analysis]), if 2 or more studies with consistent patient populations, interventions, and outcomes are captured among included studies. A Random-Effects approach using the Knapp-Hartang approach (100) for pair-wise comparison to attain the average intervention effect of penicillin allergy delabeling effectiveness and safety by the proposed intervention will be performed. For quasi-experimental studies that do not have a control arm, a random-effects proportional meta-analysis will be conducted (101).

Heterogeneity of results across studies will be assessed using the Chi^2 statistic and quantified using the I^2 statistic. If heterogeneity based on I^2 is found to be above 75%, the study level effect measures will be reported without a pooled estimate on the forest plot (203). Pre-defined subgroup analysis will be conducted (102) to explore heterogeneity. The subgroups will include patient sex, provider type (allergist/immunologist, pharmacist, nurse, primary care practitioner (physician or nurse practitioner), hospitalist, specialist, patient self-completed, other), and patient age (less than 65 years versus greater than or equal to 65 years of age) for the primary objective of successful delabeling as well as all secondary objectives expressed in the "outcome level" of the data extraction section will be conducted. If I^2 continues to be above 75%, a meta-analysis will not be conducted, and results will be summarized narratively.

To detect the presence of publication bias, funnel plots for each outcome and, where applicable, statistical methods such as selection models, examining the association between study size and estimated treatment effect, and meta-regression will be adopted, where indicated (204).

Discussion

Studies of patients with low risk penicillin allergies have demonstrated the effectiveness and safety of delabeling using history and oral challenge without the use of PST (49,89,124,205). This evidence was culminated in a pooled analysis from a systematic review including evidence from 13 studies with a total sample size of 1202 (range 7-328) showing that across all studies, 3.41% of those receiving a direct oral challenge experienced mild immediate or delayed reactions, there were no serious adverse reactions, and 96.5% of patients could be de-labelled (20).

However, much of the literature does not report penicillin allergy testing outcomes by sex and there is no unifying definition of "low risk" to describe the commonly used term. Therefore, it is unclear whether there is a sex and/or gender related difference in success of delabeling, continuity of delabeling, experienced adverse events, and longitudinal outcomes such as future antibiotic use and percentage of patients relabeled in future healthcare interactions. Further, the body of evidence on penicillin allergy risk stratification and delabeling has increased since the publication of the review by Cooper and Colleagues in 2021 (20).

The proposed project will provide a thorough review of the literature on the topic of penicillin allergy delabeling by history and oral challenge while considering sex and gender related predictors and outcomes, where described. Feedback from the project steering committee and from the OPEN Citizens' Council improved the objectives and intended data to be abstracted. The implementation of this co-designed approach into a clinical setting may reduce unnecessary secondary antimicrobial use, reduce adverse outcomes such as secondary infections, and empower patients and care providers with broadening the number and classes of antimicrobials that can be prescribed.

Data Extraction Levels and Categories

Study Level	
Descriptive	Study title, first author, study design, setting, funding sources, required checkbox "does not require penicillin skin testing prior to other forms of delabeling", includes "low risk" participants as defined by study authors, include definition of "low risk", publication status (published or unpublished), aim of study, noted protocol deviations, study limitations
Dichotomous/ Categorical	Country of study conduct, single or multi-center
Continuous	Year of publication, sample size
Patient Level	
Descriptive	Patient characteristics (population, inclusion, and exclusion criteria), demographics (sex, age, ethnicity), details regarding initial β-lactam allergic reaction
Dichotomous/ Categorical	Type of reported reaction at baseline leading to penicillin allergy label, age at time of reaction, years prior to presentation that reaction occurred
Continuous	Number of participants with reported penicillin allergy, number of participants with penicillin allergy label in each arm at baseline and number of participants who completed study intervention
Intervention Level	
Descriptive	Provider who delivered the intervention (allergist/immunologist, pharmacist, nurse, primary care practitioner (physician or nurse practitioner), hospitalist, specialist, patient self-completed, other)
Dichotomous/ Categorical	Type of intervention (history/questionnaire, oral challenge, skin testing)
Continuous	Not applicable
Outcome Level	
Descriptive	Class of antibiotics used, antibiotic appropriateness, type of reaction and treatment (if reaction occurred) with delabeling, prescriber practice changes over time
Dichotomous/ Categorical	Cost of therapy and cost-effectiveness secondary to implemented intervention, rates of reinfection, rates of readmission, rates of *C. difficile* infection, rates of multidrug resistant organism (MDRO), continuity of delabeling over time, length of hospital stay, in-hospital mortality and post-discharge mortality, readmission rates with infective diagnosis
Continuous	Percentage of successfully delabeled penicillin allergies, duration of intravenous antibiotic therapy, total number of antibiotics used

Appendix B: PRISMA-P 2015 Checklist for Systematic Reviews

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	79
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	11- 12
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	594-696
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	293- 294
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	589
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☒	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	142-146
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	164-167
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	183-200
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	227-231
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	647-680
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	155-162
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	247-252
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	290-294
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	277-285
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	269-287
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	254-265
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	303-307
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	298-307
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	309-316
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	324
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	318-320
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	325-326

Appendix C: PubMed Search Strategy

PUBMED

MARCH 30, 2022

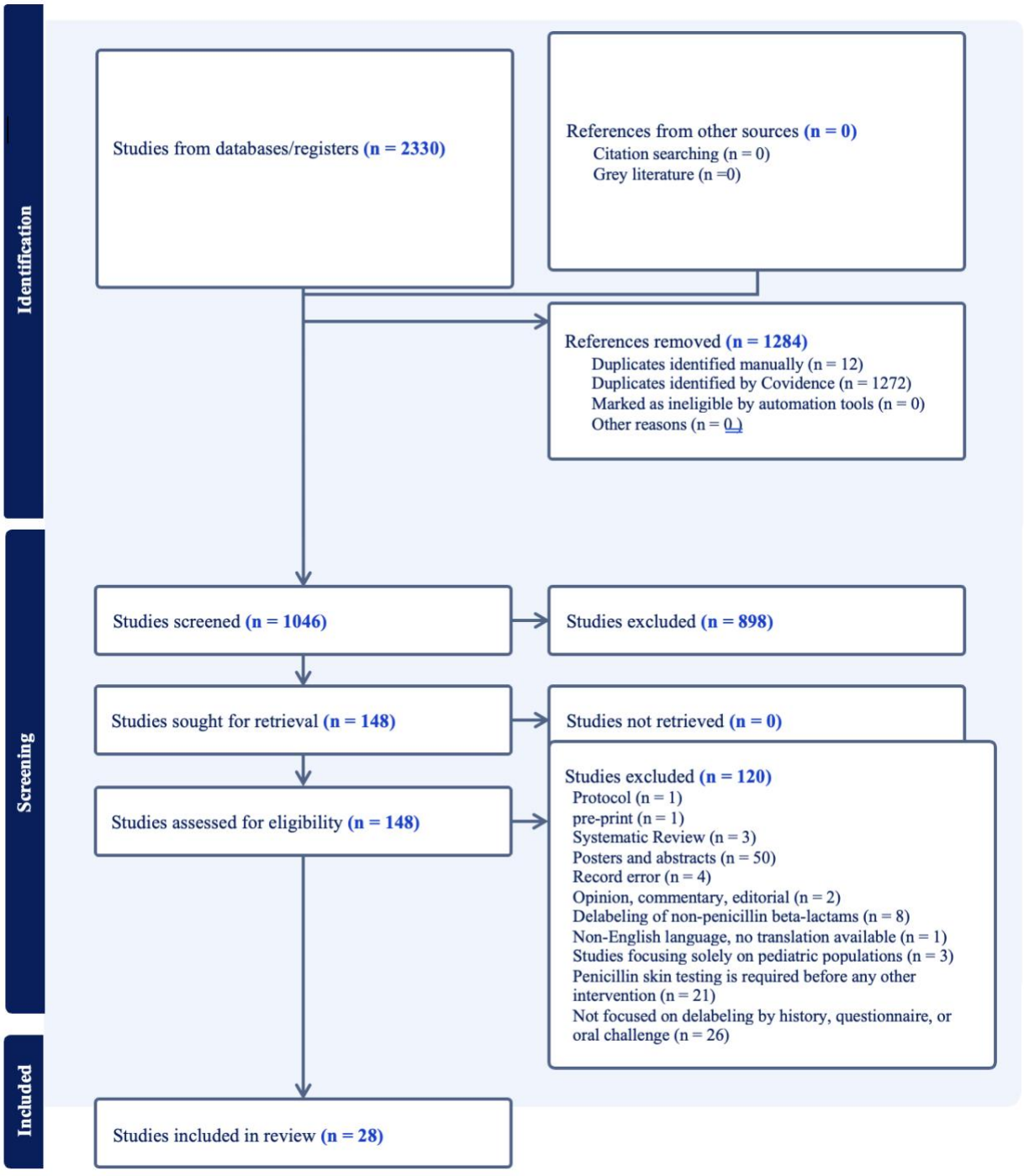
Search: ((((((("Penicillins"[nm]) OR (β-lactam*[Title/Abstract] OR "beta lactam" [Title/Abstract] OR penicillin*[Title/Abstract])) OR ("Penicillins/adverse effects"[Mesh])) AND (allerg*[Title/Abstract] OR hypersensitiv*[Title/Abstract])) AND (((direct[Title/Abstract] OR oral[Title/Abstract]) AND (challenge*[Title/Abstract] OR provocation[Title/Abstract] OR provoked[Title/Abstract])) OR (de-label*[Title/Abstract] OR label*[Title/Abstract] OR delabel*[Title/Abstract]))) NOT (children[Title] OR paediatric*[Title] OR pediatric*[Title])) AND ((((((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])) OR ((prognos*[Title/Abstract] OR (first[Title/Abstract] AND episode[Title/Abstract]) OR cohort[Title/Abstract]))) OR (((relative[Title/Abstract] AND risk*[Title/Abstract]) OR (relative risk[Text Word]) OR risks[Text Word] OR cohort studies[MeSH:noexp] OR (cohort[Title/Abstract] AND study[Title/Abstract]) OR (cohort[Title/Abstract] AND studies[Title/Abstract])))) OR ((((systematic review[ti] OR systematic literature review[ti] OR systematic scoping review[ti] OR systematic narrative review[ti] OR systematic qualitative review[ti] OR systematic evidence review[ti] OR systematic quantitative review[ti] OR systematic meta-review[ti] OR systematic critical review[ti] OR systematic mixed studies review[ti] OR systematic mapping review[ti] OR systematic cochrane review[ti] OR systematic search and review[ti] OR systematic integrative review[ti] OR meta-analysis OR "meta analysis" OR "meta regress*" OR meta-regress*) NOT comment[pt] NOT (protocol[ti] OR protocols[ti])) NOT MEDLINE [subset]) OR (Cochrane Database Syst Rev[ta] AND review[pt]) OR systematic review[pt]))

Results: 279

Search Update: June 13, 2023 [last search March 23 2022; search date range 2022 – present] Results: 95

Search update: October 2, 2023 [2022 – 2024] Results: 123

Appendix D: PRISMA Diagram



Appendix E: Proportion of Female Participants in Included Studies

First Author	Year	Number of Females	% Females	Mean (SD) age
Tucker	2017	NR	NR	NR
Trubiano	2018	25	54%	56 (32)[T]
duPlessis	2019	156	62%	65 (30) [T]
Iammatteo	2019	120	77%	52 (NR)
Mustafa	2019	246	68%	35 (25)
Savic	2019	NR	NR	NR
Devchand	2019	65	61%	68 (22) [T]
Kuruvilla	2019	40	80%	59 (63) [TT]
Ramsey	2020	34	71%	65 (16)
Stevenson	2020	93	56%	42 (76) [T]
Chau	2021	738	60%	66 (26)[T]
Gateman	2021	72	73%	43 (16)
Sneddon	2021	68	61%	61 (18)
Zhang	2021	28	100%	35 (5)
Song	2021	NR	NR	NR
Ham	2021	34	68%	58 (66) [TT]
Steenvoorden	2021	33	58%	68 (19)
Livirya	2022	115	71%	73 (NR)
Koo	2022	93	45%	58 (21) [T]
Fanizza	2022	34	49%	70 (75) [T]
Trubiano	2022	767	57%	66 (NR)
Mak	2022	216	100%	34 (4)
Fransson	2022	134	66%	50 (24) [T]
Copaescu	2023	116	62%	52 (28)[T]
Rozario	2023	44	54%	64 (NR)
Wade	2023	NR	NR	NR
Stollings	2023	9	38%	62 (14)[T]
Alnaes	2023	92	62%	48 (74)[T T]

Legend:

IQR: Interquartile Range; NR: Not Reported; SD: Standard Deviation

[T] Median (IQR), [TT] Median (range)

Appendix F: Effective Public Health Practice Project Quality Assessment Tool

First Author	Year	Selection Bias	Study Design	Confounders	Blinding	Data Collection Method	Withdrawals and Dropouts	Overall
Alnæs MB	2023	🔴	🔴	🔴	🔴	🔴	N/A	🔴
Chua, K	2021	🟡	🔴	🟢	🔴	🟡	N/A	🔴
Copaescu, A	2023	🟢	🟢	🔴	🟡	🟢	🟢	🟡
Devchand, M	2019	🟢	🔴	🔴	🔴	🟡	N/A	🔴
duPlessis, T	2019	🟡	🔴	🔴	🔴	🔴	🟢	🔴
Fanizza FA	2022	🟡	🔴	🔴	🟡	🔴	N/A	🔴
Fransson, S	2022	🟡	🔴	🔴	🟡	🔴	🔴	🔴
Gateman, DP	2021	🟢	🔴	🔴	🟡	🔴	N/A	🔴
Ham, Y	2021	🔴	🔴	🔴	🟡	🔴	N/A	🔴
Iammatteo, M	2019	🟡	🟢	🔴	🔴	🔴	🟢	🔴
Koo, G	2022	🟢	🔴	🔴	🟡	🔴	N/A	🔴
Kuruvilla, M	2019	🟡	🔴	🔴	🟡	🔴	N/A	🔴
Livirya, S	2022	🔴	🔴	🔴	🔴	🔴	N/A	🔴
Mak, R	2022	🔴	🔴	🔴	🟡	🟢	N/A	🔴
Mustafa, S	2019	🔴	🟢	🔴	🔴	🔴	🟡	🔴
Ramsey, A	2020	🔴	🔴	🔴	🔴	🔴	N/A	🔴
Rozario, C	2023	🟡	🔴	🔴	🟡	🔴	N/A	🔴
Savic, L	2019	🔴	🔴	🔴	🔴	🔴	🟡	🔴
Sneddon, J	2021	🟡	🔴	🔴	🔴	🔴	🔴	🔴
Song, YC	2021	🔴	🔴	🔴	🔴	🔴	🔴	🔴
Steenvoorden, L	2021	🟡	🔴	🔴	🔴	🔴	N/A	🔴
Stevenson, B	2020	🟡	🔴	🟡	🔴	🔴	N/A	🔴
Stollings, J	2023	🟡	🔴	🔴	🟡	🟡	N/A	🔴
Trubiano, J	2022	🟡	🔴	🔴	🔴	🟡	N/A	🔴
Trubiano, JA	2018	🟡	🔴	🔴	🟡	🔴	N/A	🔴
Tucker, MH	2017	🔴	🔴	🔴	🔴	🔴	N/A	🔴
Wade, S	2023	🔴	🔴	🔴	🔴	🟡	🔴	🔴
Zhang, BY	2021	🔴	🔴	🔴	🟡	🔴	🔴	🔴

Legend	Colour
Strong	🟢
Moderate	🟡
Weak	🔴

Appendix G: Definitions of Low-Risk Penicillin Allergy

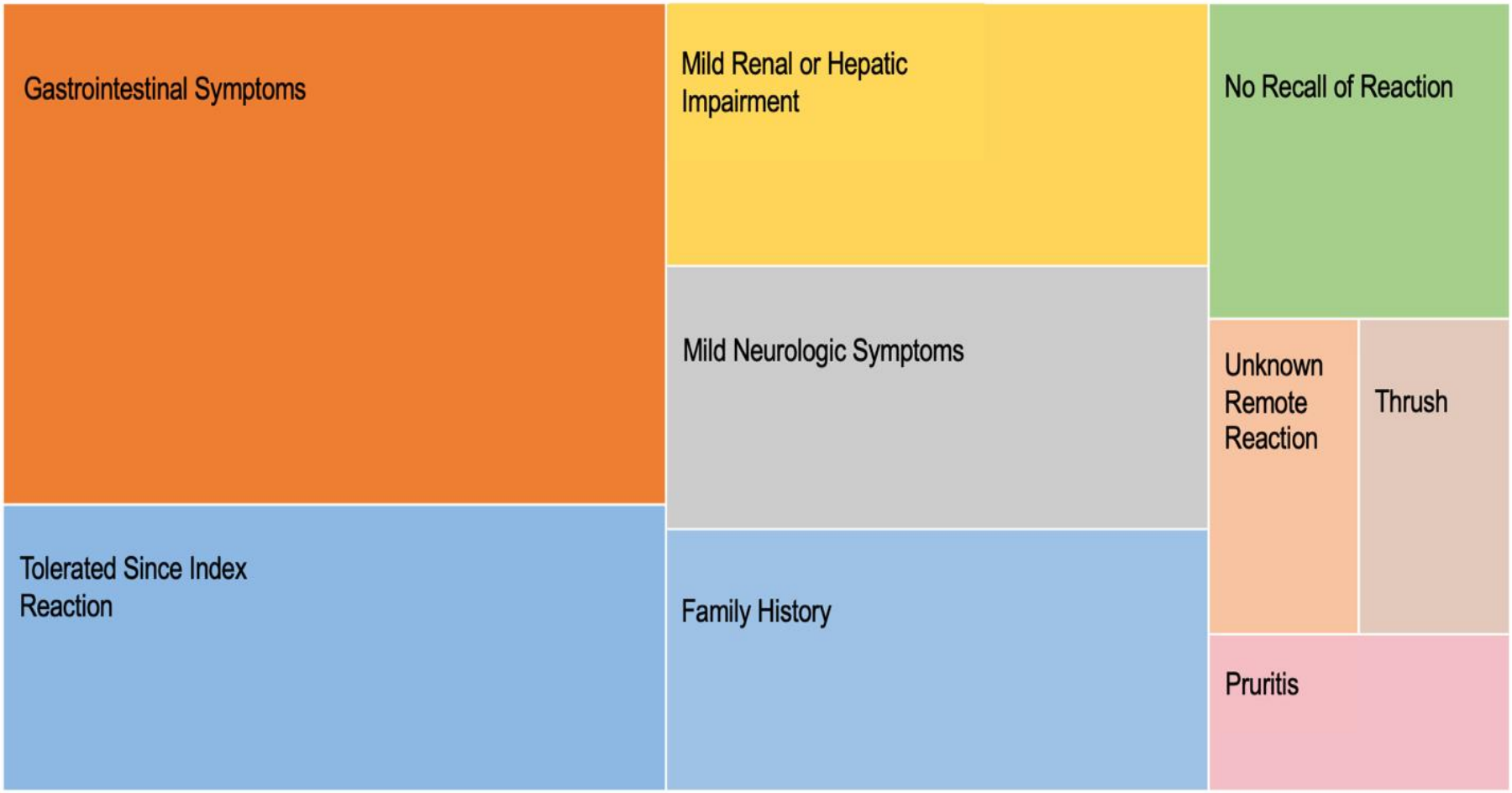
Author	year	Low Risk Only?	Definition of low risk	Reviewer Comments
Tucker	2017	Yes	Not provided	Uncertain if the baseline prevalence is all those with a reported penicillin allergy (unclear selection criteria)
Trubiano	2018	Yes	Unknown reaction >10 years before, a type A adverse drug reaction (ADR; pharmacologically predictable drug side effect or intolerance), or a history of a benign childhood rash, non-urticarial rash, or maculopapular exanthem more than 10 years ago	98 of the 195 reviewed patients were considered low risk. 46 underwent oral challenge, 2 refused, 50 met exclusion criteria
Devchand	2019	Yes	**Direct delabel**: renal impairment (does not meet criteria for renal failure or severe injury), hepatic enzyme derangement (does not meet criteria for liver failure or severe injury), gastrointestinal symptoms (nausea, vomiting, diarrhea), neurological or CNS manifestation (headache, optic neuritis, confusion, depression, mood disorder, low mood, psychosis) **Oral challenge:** childhood exanthem (unspecified)-details of rash timing unknown and no severe features or hospitaization, diffuse rash or localized rash with no other symptoms >24 hours post starting antibiotic >10 years ago, unknown reaction >10 years ago or family history of penicillin allergy only	20 of 21 patients consented to oral challenge and all were successfully delabeled
duPlessis	2019	No	**Direct delabel:** allergy label removed from their medical record if the interview clearly revealed their 'allergy' was not consistent with a true immediate hypersensitivity reaction. **Oral challenge:** penicillin 'allergy' was likely to be a delayed-type reaction (e.g. delayed onset rash).	All three patients with reaction had rash
Iammatteo	2019	yes	Patients 7 years old with historical non-life-threatening reactions to penicillin were eligible for inclusion	165 patients were screened and 159 were enrolled of whom 3 discontinued the challenge and 1 withdrew. 155 were included in the analysis. 31 patients (20%) experienced nonallergic reactions to either placebo (n=16) or amoxicillin (n=15) and 4 patients (2.6%) developed allergic reactions.
Kuruvilla	2019	Yes	**Oral challenge:** History of benign rash or benign somatic symptoms, or unknown history associated with their last penicillin exposure if it occurred >12 months ago. **Direct Delabel:** In patients with stated reaction only GI upset and those who received penicillin since the original label, were de-labeled based on history and not offered OC.	50 patients out of 355 seen by allergist had a PAL (14%). 20 patients consented to oral challenge and 18 declined
Mustafa	2019	No	**OC vs PST**: skin rash, hives, itching, or unknown reaction >10 years ago with no other history **Direct delabel:** gastrointestinal symptoms only, family history of reaction without a personal history	Of the 2465 patients included, 363 reported penicillin allergy (14.7%). 159 patients were included in the analysis of which 80 were offered PST and 79 OC
Savic	2019	Yes	Low risk defined as: nausea/ vomiting/ diarrhea, non-itchy rash, thrush, not admitted to hospital, do not know/cannot remember	74 of the 219 patients screened were eligible for testing (34%). Of the 74 patients, 18 failed to attend clinic. Of those tested, none had immediate adverse reactions. One patient developed urticaria after second dose and stopped taking amoxicillin.
Ramsey	2020	No	**Direct delabel:** gastrointestinal symptoms only, family history of a reaction without a personal history of reaction **Oral challenge:** history of a cutaneous-only reaction including non-specific rash, itching, or urticaria or an unknown reaction history more than 20 years ago were offered a 3-step DC to amoxicillin.	None

Stevenson	2020	Yes	Heterogenous per study authors "What constituted a low-risk history was left open to clinician interpretation.'	Only reports those that underwent OC not those eligible. 112 patients were grouped as optimal low risk definition (Table E4)
Chua	2021	Yes	**Direct delabel:** Mild renal or hepatic impairment (non-immune related), GI symptoms (nausea, diarrhea, vomiting), Mild neurologic symptoms (headache, depression, mood disorder) **Oral Challenge:** Childhood exanthem (mild rash, no severe features), Diffuse rash or localized rash/swelling (no other symptoms, non-immediate or unknown timing) occurred greater than 10 years ago), Unknown reaction (more than 10 years ago)	In the overall cohort, 1,272 patients reported a penicillin allergy and of these 1,225 were included in the analysis. Of these 558 were considered low risk.
Gateman	2021	Yes	No history of anaphylaxis or severe cutaneous reactions.	3 reactions occurred but only in the pediatric population
Ham	2021	No	**Low-risk:** mild and did not seem to be immunoglobulin E (IgE) mediated, if the patient did not remember the reaction, or if an IgE-mediated reaction occurred >10 years ago.	3,000 individuals with a penicillin allergy in medical record of approximately 24,000 hospital admissions. 50 patients who underwent delabeling were considered the only low risk population but were those with data in the study
Sneddon	2021	Yes	Patients with a reported penicillin allergy or record of penicillin allergy in notes without a history suggestive of Type IV hypersensitivity or Type I hypersensitivity or those without a reaction that occurred within the last 10 years, required admission or urgent treatment or a reaction that occurred within an hour of drug administration were deemed low risk	92 consented to oral challenge, 3 did not consent but were eligible
Song	2021	No	**Direct delabeling:** Family history, itching without rash (pruritis), unknown remote (>10 yrs ago) reaction, patient denies allergy but is on record	Study focused on delabeling only. Of the 66 patients included in the study, 50 were considered to have a true allergy and therefore not low risk
Steenvoorden	2021	Yes	Patient has a history of benign rash, symptoms unlikely to be of allergic etiology (headache, mild GI symptoms), or no recollection of the reaction	During the two study periods, 5,529 unique patients were admitted to the medical department. 257 of these (4.6%) reported a penicillin allergy**.** Results are conflicting - in abstract and figure 1 the denominator is 54, but in the results, it is 57.
Zhang	2021	Yes	**Direct delabel:** has the medication been taken since initial reaction and tolerated **Oral challenge:** reaction more than 5 years ago and no severe systemic or cutaneous adverse drug reactions or immediate symptoms (urticaria, wheezing, dizziness etc),	148 patients referred, 24 evaluated in phase 1 and 42 in phase 2. 28 considered low risk
Fanizza	2022	yes	**2-step challenge:** Patients that did not have a history of IgE-mediated reaction to a PCN antibiotic were a candidate for testing if they met any of the following criteria: a history of benign rash (without IgE involvement), an unknown reaction without features of IgE-mediated reactions, benign somatic symptoms unlikely to be allergic (e.g., gastrointestinal symptoms or headache), or a family history of allergic reaction to any antibiotic in the PCN class. **3-step** (scratch test, intradermal, then OC): history of an IgE-mediated reaction to any antibiotic in the PCN class	72 patients were referred, 70 completed the challenge. Outcomes for sex, age, etc. were not defined for just the very low risk (or 2-step challenge directly)
Fransson	2022	Yes	**Penicillin Allergy Unlikely:** mild nonallergic symptoms, (e.g. headache, gastrointestinal symptoms), no personal history of an allergic reaction **Low Risk:** single suspected allergic reaction, onset of symptoms >2h after first dose, benign skin symptoms defined as uncharacterized exanthema, flushing, light pruritus, or/and maculopapular exanthema lasting <7 days, unknown/sparse information about index reaction	Data from the prospective population. Out of the 202 patients, 20 (10%, CI: 7%–15%) had a positive DPT, but none (0/202, 0%, CI: 0%–2%) had anaphylaxis or a severe delayed hypersensitivity reaction. In the retrospective population, 183 of 1759 patients were deemed to be allergic (from supplementary Table 1)

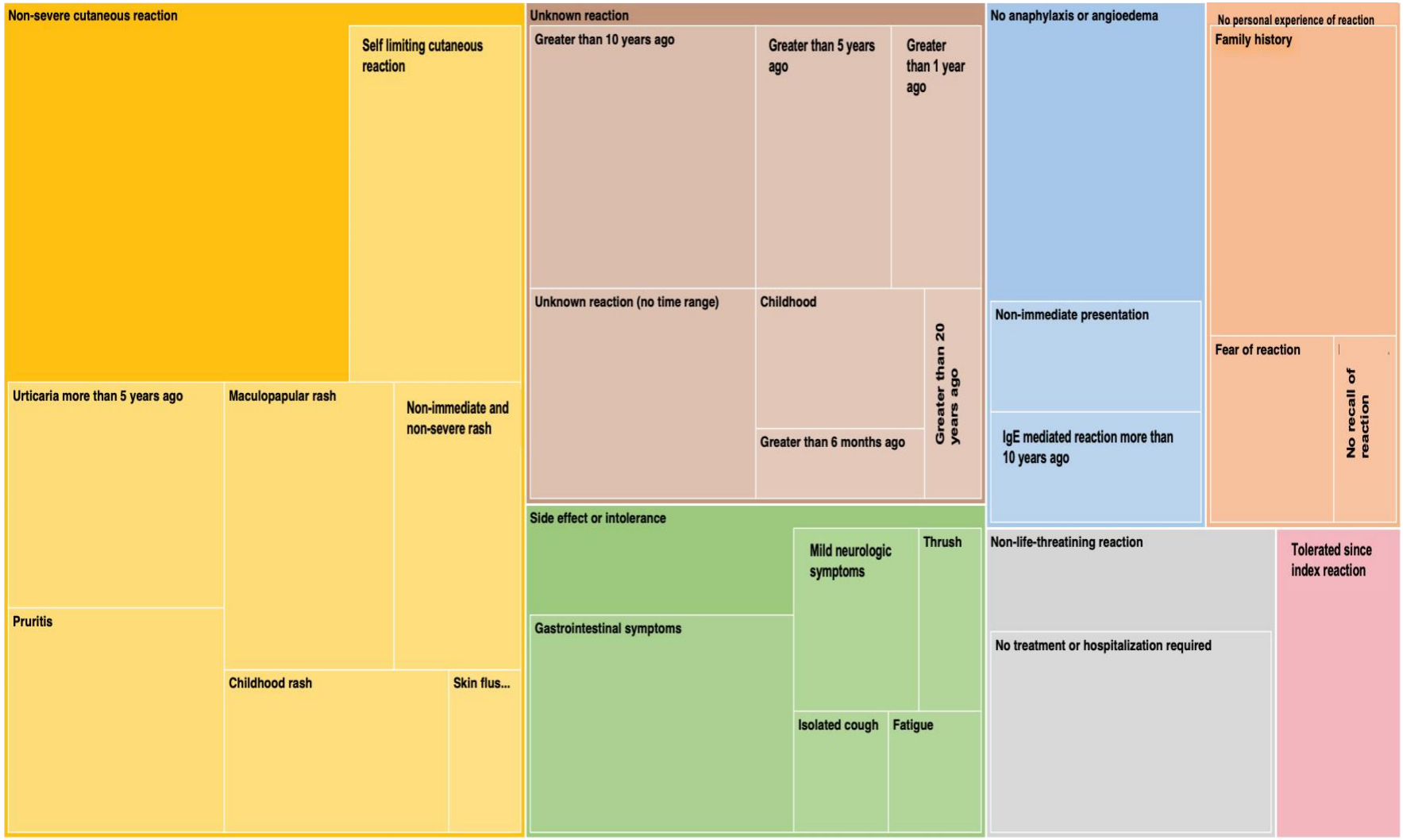
Koo	2022	yes	Isolated urticaria more than 5 years ago, self-limited cutaneous rash at any point in the past without any organ involvement or signs of a severe delayed rash, gastrointestinal symptoms only, remote childhood reaction with limited details, family history of penicillin allergy only, avoidant from fear of allergy only, known tolerance of a penicillin since the original reaction occurred, or other non-allergy symptoms.	240 patients were 28.6% of MICU patients over the period of the study with a PAL. 205 patients agreed to oral challenge, and all passed initial challenge but 2 had delayed reaction. Sex reported by challenge performed vs declined but it is unclear if the patients with reactions were male or female.
Livirya	2022	No	**Oral Challenge:** A limited cutaneous reaction (including rash and hives), or unknown symptoms occurring ≥6 months ago and ≥1 h after drug administration, and suitable for an oral challenge. **Direct Delabel**: Patients with a history of a mild ADR such as gastrointestinal (GI) upset, or those who had received penicillin antibiotics after their index reaction, were de-labelled without challenge	Prevalence of penicillin allergy was 289/1,763 records (16.4%). 79 patients were eligible for oral challenge, 38 declined.
Mak	2022	Yes	Patients with a PEN-FAST score of 0 were classified as very low-risk and were offered DOC.	
Trubiano	2022	yes	Defined in a protocol paper by Chua and colleagues	Authors describe that 47.8% of the 1,336 patients were low risk but do not give a sample size for this- calculated by hand to be 638.6 rounded to 639
Alnaes	2023	No	**Very low risk:** received the same penicillin again without reaction, family members with a penicillin allergy, the patient has never reacted, exclusively gastrointestinal upset from penicillin intake **Low risk: u**nknown reaction >10 years ago, patient denies a penicillin allergy, but it is noted in the electronic patient record, fatigue, isolated cough, rash with erythema/macule/papules (maculopapular exanthema), isolated itch	16 were very low risk and underwent direct challenge, 58 low risk underwent direct challenge with 1 having a reaction
Copaescu	2023	Yes	PEN-FAST Score <3	192 allocated to PST then OC. 2 did not receive challenge following PST. 176 were included in the per protocol analysis 188 received OC, 13 excluded due to protocol violation, 175 included in per-protocol analysis
Rozario	2023	yes	History of cutaneous reactions only more than 1 year ago or unknown reactions more than 1 year ago.	All 81 patients met criteria for low-risk categorization and among them, 98% (79 of 81) tolerated direct challenge
Stollings	2023	Yes	Urticaria only more than 5 years ago, self-limited cutaneous rash at any point in the past without any organ involvement or signs of a severe delayed rash, GI symptoms only, Remote childhood reaction with limited details, family history of penicillin allergy, avoidant from fear of allergy only, known tolerance of a penicillin since the original reaction occurred, other nonallergy symptoms	2670 COVID-positive patients were admitted to our MICU. Penicillin allergies were identified in 285 (10.6%) of these patients. Population had to have recently stabilized COVID-19 and low-risk penicillin allergy. 19 of 24 patients accepted the oral challenge.
Wade	2023	No	**Direct delabeling:** Gastrointestinal symptoms (nausea, vomiting, diarrhoea), Neurological or CNS manifestation (headache, optic neuritis, confusion, depression, mood disorder, low mood, psychosis), Hepatic enzyme derangement (does not include liver failure of severe liver injury), Renal impairment (does not include renal failure or severe injury), Reports family history of penicillin allergy only, Oral candidiasis reported ('thrush'), Patient reports an allergy but has since tolerated penicillin-based antibiotic	164 patients were considered, 1 died and removed from analysis, 29 were direct delabel, 71 were low risk and eligible for oral challenge (not included in this study). Authors describe that 29 could be directly delabeled, but only 21 consented

Legend:
ADR: Adverse Drug Reaction; CNS: Central Nervous System; PAL: Penicillin Allergy Label; OC: Oral Challenge; PST: Penicillin Skin Test; GI: Gastrointestinal; PCN: Penicillin; MICU: Medical Intensive Care Unit

Appendix H: Direct Delabel Themes within Definitions of Low-Risk Across 11 Studies



Appendix I: Oral Challenge Themes within Definitions of Low-Risk Across 26 Studies



Appendix J: Reported Reactions to OC (26 Studies)

First author	Number (%) of reactions on oral challenge	Comments
Alnaes	1 (1%)	Non-severe rash
Chau	9 (5%)	Six patients had a positive oral challenge, and 3 patients reported a non-immune- mediated reaction to oral challenge (1 fever [38.1°C, concurrent urosepsis], 1 vomiting, and 1 pruritis without rash)
Copaescu	1 (1%)	1 immune mediated reaction in both the OC and PST arms
Devchand	NR	No follow up once delabeling completed
duPlessis	3 (9%)	Of those with a reaction on direct delabel, the reactions were nausea, vomiting or headache
Fanizza	0 (0%)	No reactions were described for patients in the oral challenge arm
Fransson	20 (10%)	19 cutaneous symptoms, 1 hyperventilation. 13 of 19 individuals with cutaneous reactions experienced symptoms 3 days after OC
Gateman	3 (3%)	3 pediatric patients had a reaction, none of the adult patients had a reaction
Ham	2 (7%)	Two patients retained their allergy label due to mild reactions in the two-step challenge
Iammatteo	19 (12%)	16 people experienced a reaction to placebo, not included in reaction to oral challenge. Of those with reaction to oral challenge, 4 were allergic and 15 were non-allergic reaction types but included in this table
Koo	NR	
Kuruvilla	3 (15%)	3 reactions reported: chest tightness, pruritis and dizziness. All resolved within minutes and no treatment required, not considered a positive reaction in this study
Livirya	4 (10%)	Description of reactions not reported. Relabeling on follow-up
Mak	4 (2%)	No immediate hypersensitivity, 4 delayed cutaneous reactions, 1 vomiting (unrelated to challenge)
Mustafa	3 (4%)	No reactions in PST arm, 3 cutaneous reactions (treated with antihistamines) in OC arm
Ramsey	3 (6%)	1 rash with amoxicillin/clavulanate on day 17 of therapy (10 days after discharge), 1 facial swelling and nausea/vomiting with amoxicillin/clavulanate on the day after the challenge, and 1 from the PST group experienced a rash with cefazolin on day 17 of cefazolin therapy
Rozario	2 (2%)	Of the 79 patients who were delabeled, allergy label was only removed from EMR for 64 (81%) and 2 cases of delayed reactions were noted
Savic	1 (2%)	One patient developed urticaria in her hands after the second dose and stopped taking the amoxicillin. On questioning, it was discovered that her index reaction had been of widespread urticaria, but she had chosen not to disclose this to the study team previously as she was keen to be tested
Sneddon	1 (1%)	1 patient did not have a documented success or failure rate and was therefore deemed non-successful, but no reaction was reported
Steenvoorden	2 (4%)	1 admitted patient had worsening of ongoing bronchial obstruction symptoms, resolved with ipratropium bromide-salbutamol inhalation. This patient could not be delabeled although likely not an IgE reaction. One other patient reported a mild maculopapular rash 2 days after oral challenge - no need for treatment and was delabeled
Stevenson	6 (4%)	Direct challenge was performed for both low and moderate risk and described in the supplementary material
Stollings	NR	No oral challenge completed
Trubiano	20 (4%)	10 immune mediated (9 delayed rash, 1 immediate rash, 1 decreased consciousness, 1 self-resolving throat tightness, 1 fever, and 1 unknown); none required epinephrine) and 10 non-immune mediated.
Trubiano	0 (0%)	All patients who received the oral challenge tolerated it
Tucker	5 (2%)	Description of reactions not reported.
Zhang	NR	No reactions reported

Legend
NR: None Reported; OC: Oral Challenge; PST: Penicillin Skin Test; EMR: Electronic Medical Record

Appendix K: List of Penicillins

Aminopenicillins	Amoxicillin
	Amoxicillin-clavulanate
	Ampicillin
	Ampicillin-sulbactam
Antipseudomonal penicillin	Piperacillin-tazobactam
Anti-staphylococcal penicillins	Cloxacillin
	Dicloxacillin
	Flucloxacillin
	Nafcillin
	Oxacillin
Natural penicillins	Penicillin G
	Penicillin VK

Appendix L: List of Non-Penicillin B-Lactams

Antimicrobial Class	Antimicrobial
Cephalosporins	Cefazolin
	Cefadroxil
	Cephalexin
	Cefuroxime-axetil
	Cefprozil
	Cefuroxime
	Cefoxitin
	Cefotaxime
	Ceftriaxone
	Ceftazidime
	Cefixime
	Cefepime
	Ceftobiprole
Carbapenems	Meropenem
	Imipenem-cilastin
	Ertapenem
Monobactam	Aztreonam

Appendix M: Comorbidities Assessed for Correlation with Penicillin Allergy Label Presence

Atopic Conditions
"Atopic dermatitis" = c("L20.0", "L20.8", "L20.9"), "Asthma" = c("J45.0", "J45.1", "J45.8", "J45.9"), "Seasonal allergic rhinitis" = c("J30.0", "J30.2", "J30.3", "J30.4"), "Eczema" = c("J30.1","L30.8", "L30.9"),
Autoimmune Conditions
"Adult-onset Still disease" = c("M06.1"), "Ankylosing Spondylitis" = c("M45"), "Antiphospholipid Syndrome" = c("D68.8"), "Autoimmune thyroiditis" = c("E06.3"), "Dermatomyositis" = c("M33.1"), "Granulomatosis with Polyangiitis" = c("M31.3"), "Graves' Disease" = c("E05.0", "E05.0, H58.8", "E05.0"), "Guillain-Barré syndrome" = c("G61.0"), "Lupus erythematosus" = c("M32.0", "M32.1", "M32.8", "M32.9", "D59.1, M32.9", "L93.0", "L93.2", "M32.1, G05.8"), "Multiple sclerosis" = c("G35"), "Myasthenia gravis" = c("G70.0"), "Necrotizing vasculopathies" = c("M31.0"), "Psoriatic and enteropathic arthropathies" = c("L40.5, M07.3", "A09.9, M07.6"), "Rheumatoid Arthritis" = c("M05.3", "M05.9", "M06.0", "M06.9", "M08.0"), "Sarcoidosis" = c("D86.0", "D86.1", "D86.2", "D86.3", "D86.8"), "Sjögren syndrome" = c("M35.0"), "Scleroderma" = c("M34.0", "M34.1", "M34.2", "M34.8", "M34.9"), "Type 1 diabetes mellitus" = c("E10.23, N08.35", "E10.30, H36.0", "E10.63", "E10.9", "E10.10"), "Vitiligo" = c("L80"),
Obesity
"Obesity" = c("E66.0", "E66.1", "E66.2", "E66.8", "E66.9")

Appendix N: Sex-Stratified Comorbidities as Predictors of Penicillin Allergy Label Presence

Category	Condition	Female Unadjusted OR (95% CI)	Male Unadjusted OR (95% CI)	Female p value (Categorical)	Male p value (Categorical)
Atopic Conditions		2.06 (1.81-2.34)	1.93 (1.50-2.46)	<0.001	<0.001
	Atopic dermatitis	1.72 (0.45-4.92)	1.73 (0.19-7.08)	=0.39	=0.55
	Asthma	2.14 (1.87-2.44)	2.09 (1.61-2.68)	<0.001	<0.001
	Seasonal allergic rhinitis	2.21 (1.21-3.8)	1.04 (0.21-3.09)	<0.05	=0.96
	Eczema	1.5 (1.02-2.15)	2 (0.91-3.88)	<0.05	=0.083
Autoimmune Inflammatory Conditions		1.75 (1.49-2.04)	1.42 (0.97-2.01)	<0.001	=0.06
	Adult-onset still disease	1.52 (0.01-18.7)	na	=0.8	na
	Ankylosing spondylitis	2.3 (1.05-4.58)	1.78 (0.57-4.26)	<0.05	=0.28
	Antiphospholipid syndrome	2.74 (0.83-7.55)	1.2 (0.01-10.14)	=0.094	=0.9
	Autoimmune thyroiditis	1.33 (0.69-2.34)	1.04 (0.01-8.52)	=0.37	=0.98
	Dermatomyositis	1.97 (0.51-5.78)	6.68 (0.65-40.66)	=0.29	=0.097
	Granulomatosis with polyangiitis	3.46 (0.62-14.35)	2.22 (0.02-22.96)	=0.14	=0.63
	Graves' disease	1.3 (0.86-1.9)	1.92 (0.62-4.63)	=0.2	=0.23
	Guillain-barré syndrome	0.4 (0-3.15)	0.68 (0.01-5.19)	=0.47	=0.77
	Lupus erythematosus	3.29 (2.14-4.96)	0.82 (0.01-6.45)	<0.001	=0.89
	Multiple sclerosis	1.81 (0.9-3.32)	4.05 (1.04-11.88)	=0.091	<0.05
	Myasthenia gravis	2.54 (1.03-5.56)	1.42 (0.16-5.65)	<0.05	=0.7
	Necrotizing vasculopathies	0.58 (0-4.95)	6.68 (0.65-40.66)	=0.69	=0.097
	Psoriatic and enteropathic arthropathies	1.58 (0.79-2.87)	2.07 (0.75-4.65)	=0.18	=0.14
	Rheumatoid arthritis	1.9 (1.4-2.54)	1.13 (0.42-2.47)	<0.001	=0.78
	Sarcoidosis	1.32 (0.52-2.84)	1.2 (0.13-4.69)	=0.53	=0.84
	Scleroderma	1.12 (0.4-2.52)	1.04 (0.01-8.52)	=0.81	=0.98
	Sjögren syndrome	2.64 (1.54-4.35)	6.68 (0.65-40.66)	<0.001	=0.097
	Type 1 diabetes mellitus	1.56 (0.95-2.43)	1.92 (0.91-3.59)	=0.077	=0.083
	Vitiligo	1.52 (0.6-3.31)	1.42 (0.16-5.65)	=0.35	=0.7
Metabolic Conditions		1.38 (0.99-1.88)	1. 82 (1.07-2.90)	=0.05	<0.05
	Obesity	1.39 (1-1.89)	1.86 (1.11-2.95)	=0.051	<0.05

Appendix O: Antibiotic Classifications as Coded in R Studio

Antibiotic classification	**Vector in R Studio**
Penicillins	penicillins <- c("AMOXICILLIN", "AMOXICILLIN CLAVULANATE", "AMPICILLIN", "CLOXACILLIN", "PENICILLIN", "PIPERACILLIN TAZOBACTAM")
Cephalosporins	cephalosporins <- c("CEFACLOR", "CEFADROXIL", "CEFAZOLIN", "CEFIXIME", "CEFPROZIL", "CEFTAZIDIME", "CEFTRIAXONE", "CEFUROXIME", "CEPHALEXIN")
Carbapenems	carbapenems <- c("ERTAPENEM", "MEROPENEM")
Macrolides	macrolides <- c("AZITHROMYCIN", "CLARITHROMYCIN", "ERYTHROMYCIN")
Fluoroquinolones	fluoroquinolones <- c("CIPROFLOXACIN", "LEVOFLOXACIN", "MOXIFLOXACIN", "NORFLOXACIN",

	"OFLOXACIN")
Tetracyclines	tetracyclines <- c("DOXYCYCLINE", "MINOCYCLINE", "TETRACYCLINE")
Topical Antimicrobials	topical <- c("BACITRACIN", "BACITRACIN POLYMIXIN B", "GRAMICIDIN", "TRIAMCINOLONE NYSTATIN NEOMYCIN GRAMICIDIN", "BIODERM", "FUCIDIN", "MUPIROCIN", "TOBRAMYCIN DEXAMETHASONE", "SILVER SULFASALAZINE")
Aminoglycosides	aminoglycosides <- c("TOBRAMYCIN")
Lincosamides and Glycopeptides	lincosamide_glycopeptide <-c("CLINDAMYCIN", "VANCOMYCIN")
Folate synthesis inhibitors	folate_synthesis_inhibitor <- c("DAPSONE", "SULFAMETHOXAZOLE TRIMETHOPRIM")
Other	other <- c("ETHAMBUTOL", "FOSFOMYCIN", "METRONIDAZOLE", "NITROFURANTOIN", "RIFAMPIN")

Appendix P: Guideline- Concordant Antibiotic Therapy

Empiric Therapy		
Indication	**Guideline- Concordant Therapy**	**Guideline**
Febrile neutropenia, inpatient	Piperacillin-tazobactam Meropenem OR imipenem-cilastatin Ceftazidime AND vancomycin	(206)
Community acquired pneumonia, inpatient	Beta-lactam and macrolide OR Respiratory fluoroquinolone	(207)
Diabetic foot infection, no MRSA	Penicillins, cephalosporins, carbapenems	(3,4,141)
Necrotizing infection, cellulitis, erysipelas	Piperacillin-tazobactam AND vancomycin	(208)
Targeted Therapy		
Indication	**Guideline- Concordant Therapy**	**Guideline**
Methicillin-susceptible *Staphylococcus aureus* bacteremia	Cloxacillin Cefazolin	(25,38)
Culture and sensitivities guided therapy	Beta-lactam is the most appropriate option	Targeted

Legend: MRSA- Methicillin Resistant *Staphylococcus aureus*

Appendix Q: ICD-10-CA Codes Organized by Disease System Using the WHO ICD-10 (Version 2019)

Disease System	WHO ICD-10 Codes Applied

Gastrointestinal and Hepatic	# ----------
	# A00–A09 Intestinal infections
	# ----------
	
	# Cholera
	cholera <- c("A00.0", "A00.1", "A00.9")
	
	# Typhoid and paratyphoid fevers
	typhoid_paratyphoid <- c("A01.0", "A01.1", "A01.2", "A01.3", "A01.4")
	
	# Salmonella infections
	salmonella <- c("A02.0", "A02.1", "A02.2", "A02.20", "A02.21", "A02.22",
	"A02.23", "A02.24", "A02.25", "A02.29", "A02.8", "A02.9")
	
	# Shigellosis
	shigellosis <- c("A03.0", "A03.1", "A03.2", "A03.3", "A03.8", "A03.9")
	
	# Clostridioides difficile enterocolitis (separate)
	clostridioides <- c("A04.7", "A04.71", "A04.72")
	
	# Other bacterial intestinal infections (excluding C. diff)
	bacterial_intestinal_other <- c("A04.0", "A04.1", "A04.2", "A04.3", "A04.4",
	"A04.5", "A04.6", "A04.8", "A04.9")
	
	# Foodborne bacterial intoxications
	foodborne <- c("A05.0", "A05.1", "A05.2", "A05.3", "A05.4", "A05.8", "A05.9")
	
	# Amebiasis
	amebiasis <- c("A06.0", "A06.1", "A06.2", "A06.3", "A06.4", "A06.5",

```
            "A06.6", "A06.7", "A06.8", "A06.9")

# Other protozoal intestinal diseases
protozoal <- c("A07.0", "A07.1", "A07.2", "A07.3", "A07.8", "A07.9")

# Viral and other specified intestinal infections
viral_intestinal <- c("A08.0", "A08.1", "A08.2", "A08.3", "A08.39",
                      "A08.4", "A08.5")

# Infectious gastroenteritis and colitis, unspecified
infectious_gastroenteritis_unspecified <- c("A09.0")


# ----------------------------
# Other GI-related infections
# ----------------------------

# Helicobacter pylori
helicobacter <- c("B96.81")

# Other specified bacterial agents sometimes GI
other_bacterial <- c("B96.2", "B96.3", "B96.4", "B96.5", "B96.82", "B96.89")

# Fungal gastrointestinal infections
candidiasis_gi <- c("B37.81", "B37.89", "B37.9")

# Parasitic GI infections (outside A06–A07)
toxoplasma_gi <- c("B58.81")
helminths <- c("B77",      # Ascariasis
               "B80",      # Enterobiasis
               "B81.0",    # Anisakiasis
               "B83.0", "B83.1", "B83.2", "B83.3", "B83.4", "B83.8", "B83.9")
```

	# Viral hepatitis (GI/liver system)
	Viral_Hepatitis <- c("B17.8", "B27.0", "B17.9", "B18.1", "B18.2", "B19.9") #EBV/mononucleosis, Viral hepatitis

Respiratory Tract (upper and lower)	# ----------
	# J00–J22 Acute respiratory infections
	# ----------
	
	# Acute nasopharyngitis (common cold)
	common_cold <- c("J00")
	
	# Acute sinusitis
	acute_sinusitis <- c("J01.0", "J01.1", "J01.2", "J01.3", "J01.4",
	"J01.8", "J01.9")
	
	# Acute pharyngitis
	acute_pharyngitis <- c("J02.0", # Streptococcal
	"J02.8", # Other specified
	"J02.9") # Unspecified
	
	# Acute tonsillitis
	acute_tonsillitis <- c("J03.0", "J03.8", "J03.9")
	
	# Acute laryngitis and tracheitis
	acute_laryngitis_tracheitis <- c("J04.0", "J04.1", "J04.2")
	
	# Acute obstructive laryngitis (croup) and epiglottitis
	croup_epiglottitis <- c("J05.0", "J05.1")
	
	# Acute upper respiratory infection, multiple/unspecified sites
	acute_uri_unspecified <- c("J06.0", "J06.9")
	
	# Influenza
	influenza <- c("J09.X1", "J09.X2", "J09.X3", "J09.X9", # Avian/other influenza
	"J10.0", "J10.1", "J10.8", # Flu with pneumonia/other

```
            "J11.0", "J11.1", "J11.8")              # Flu, unspecified

# Viral pneumonia
viral_pneumonia <- c("J12.0", "J12.1", "J12.2", "J12.3",
                     "J12.8", "J12.9")

# Bacterial pneumonia
bacterial_pneumonia <- c("J13",   # Pneumococcal
                         "J14",   # H. influenzae
                         "J15.0", "J15.1", "J15.2", "J15.3", "J15.4",
                         "J15.5", "J15.6", "J15.7", "J15.8", "J15.9")

# Pneumonia due to other infectious organisms
pneumonia_other <- c("J16.0", "J16.8", "J17")

# Pneumonia, unspecified organism
pneumonia_unspecified <- c("J18.0", "J18.1", "J18.2", "J18.8", "J18.9")

# Acute bronchitis
acute_bronchitis <- c("J20.0", "J20.1", "J20.2", "J20.3", "J20.4",
                      "J20.5", "J20.6", "J20.7", "J20.8", "J20.9")

# Bronchiolitis
bronchiolitis <- c("J21.0", "J21.1", "J21.8", "J21.9")

# Unspecified acute lower respiratory infection
acute_lri_unspecified <- c("J22")

# ----------------------------
# Other respiratory infections
# ----------------------------

# Tuberculosis of respiratory system
```

```
tuberculosis_respiratory <- c("A15.0", "A15.4", "A15.5", "A15.6",
                              "A15.7", "A15.8", "A15.9",
                              "A16.0", "A16.1", "A16.2", "A16.3",
                              "A16.4", "A16.5", "A16.8", "A16.9")

# Pertussis (whooping cough)
pertussis <- c("A37.0", "A37.1", "A37.8", "A37.9")

# Diphtheria
diphtheria <- c("A36.0", "A36.1", "A36.2", "A36.3", "A36.8", "A36.9")

# Other bacterial respiratory infections (agents classified elsewhere)
resp_bacterial_agents <- c("B95.0", "B95.1", "B95.2", "B95.3",
                           "B95.4", "B95.5", "B95.6", "B95.7",
                           "B96.0", "B96.1", "B96.20", "B96.29")

# Viral agents causing respiratory diseases
resp_viral_agents <- c("B97.0", "B97.1", "B97.2", "B97.3",
                       "B97.4", "B97.5", "B97.6", "B97.7", "B97.8")
# ----------------------------
# Mononucleosis
# ----------------------------
mononucleosis <- c("B27.0", "B27.1", "B27.8", "B27.9")

# ----------------------------
# Fungal respiratory infections
# ----------------------------

# Aspergillosis
aspergillosis <- c("B44.0", "B44.1", "B44.2", "B44.7", "B44.8", "B44.9")

# Candidiasis with respiratory involvement
candidiasis_respiratory <- c("B37.1", "B37.81", "B37.89", "B37.9")
```

	# Histoplasmosis
	histoplasmosis <- c("B39.0", "B39.1", "B39.2", "B39.3", "B39.4", "B39.5", "B39.9")
	
	# Coccidioidomycosis
	coccidioidomycosis <- c("B38.0", "B38.1", "B38.2", "B38.3", "B38.4", "B38.7", "B38.9")
	
	# Blastomycosis
	blastomycosis <- c("B40.0", "B40.1", "B40.2", "B40.3", "B40.7", "B40.8", "B40.9")
	
	# Paracoccidioidomycosis
	paracoccidioidomycosis <- c("B41.0", "B41.7", "B41.8", "B41.9")
	
	# Sporotrichosis (can involve lungs if disseminated)
	sporotrichosis <- c("B42.0", "B42.7", "B42.8", "B42.9")
	
	# Cryptococcosis
	cryptococcosis <- c("B45.0", "B45.1", "B45.2", "B45.3", "B45.7", "B45.8", "B45.9")

Central Nervous System	# Tuberculosis of nervous system
	tb_cns <- c("A17.0", "A17.1", "A17.8", "A17.9")
	
	# Prion/atypical viral infections
	prion_cns <- c("A81.0", "A81.1", "A81.2", "A81.8", "A81.9")
	
	# Viral encephalitis and meningitis
	viral_cns <- c("A83", "A84", "A85", "A86",
	"A87.0", "A87.1", "A87.2", "A87.8", "A87.9",
	"A88", "A89")
	
	# Herpesvirus and exanthem viruses with CNS involvement
	herpes_cns <- c("B00.3", "B00.4", "B00.89",
	"B01.0", "B01.1", "B01.8",
	"B02.0", "B02.1", "B02.8",

	"B05.0", "B05.1", "B05.2",
	"B06.0",
	"B26.0", "B26.1")
	
	# Fungal CNS infections
	fungal_cns <- c("B37.5", "B37.6",
	"B45.1",
	"B46.1",
	"B47.1",
	"B48.1", "B48.2")
	
	# Protozoal CNS infections
	protozoal_cns <- c("B50.0",
	"B58.2", "B58.8", "B58.9",
	"B60.0", "B60.3", "B60.4", "B60.8")
	
	# Bacterial meningitis (primary codes)
	bacterial_meningitis <- c("G00.0", "G00.1", "G00.2", "G00.3", "G00.8", "G00.9")
	
	# Meningitis/encephalitis in other diseases
	other_cns_infections <- c("G01", "G02", "G03", "G04", "G05",
	"G06.0", "G06.1", "G07", "G08", "G09")

Skin / mucous membrane infections	# ----------
	# Bacterial infections of skin & subcutaneous tissue (L00–L08)
	# ----------
	
	# Staphylococcal scalded skin syndrome
	staphylococcal_sss <- c("L00")
	
	# Impetigo
	impetigo <- c("L01.0", "L01.1", "L01.2", "L01.8", "L01.9")
	
	# Cutaneous abscess, furuncle, carbuncle

```
cutaneous_abscesses <- c("L02.0", "L02.1", "L02.2", "L02.3", "L02.8", "L02.9")

# Cellulitis and acute lymphangitis
cellulitis_lymphangitis <- c("L03.0", "L03.1", "L03.2", "L03.8", "L03.9")

# Acute lymphadenitis (often skin-associated)
acute_lymphadenitis <- c("L04.0", "L04.1", "L04.2", "L04.8", "L04.9")

# Other local infections of skin & subcutaneous tissue (includes hidradenitis with infection, etc.)
other_local_skin_infections <- c("L08.0", "L08.8", "L08.9")

# Master bacterial skin vector (L00-L08)
bacterial_skin <- c(staphylococcal_sss, impetigo, cutaneous_abscesses,
                    cellulitis_lymphangitis, acute_lymphadenitis, other_local_skin_infections)



# ----------------------------
# Viral infections primarily affecting skin & mucous membranes
# (avoid B00.3/B00.4 etc placed under CNS previously;
#  include mucocutaneous/dermatologic codes)
# ----------------------------

# Herpes simplex (cutaneous / mucocutaneous manifestations)
herpes_simplex_skin_mucosa <- c("B00.0", "B00.1", "B00.2", "B00.7", "B00.8", "B00.9")

# Varicella (uncomplicated/skin) and Zoster (cutaneous)
varicella_zoster_skin <- c("B01.9", "B02.0", "B02.9")  # B01.0/B02.0 were used for CNS complications earlier

# Other viral exanthem / viral warts / molluscum contagiosum
other_viral_skin <- c("B05.9",     # measles without complication (cutaneous reference)
                      "B07",       # viral warts
                      "B08.1",     # Molluscum contagiosum (and other localized viral infections of skin)
                      "B08.4")     # Other specified viral infections of skin and mucous membranes
```

```
# Master viral skin vector
viral_skin <- c(herpes_simplex_skin_mucosa, varicella_zoster_skin, other_viral_skin)

# ----------------------------
# Fungal infections of skin & mucous membranes (cutaneous mycoses)
# ----------------------------
# Dermatophytoses (tinea / ringworm)
dermatophytoses <- c("B35.0", "B35.1", "B35.2", "B35.3", "B35.4", "B35.5", "B35.6", "B35.8", "B35.9")

# Other superficial mycoses (pityriasis versicolor, etc.)
other_cutaneous_mycoses <- c("B36.0", "B36.9")

# Candidiasis of skin & nail (assigned to skin here; note GI/resp used other candidiasis codes)
candidiasis_skin <- c("B37.2")   # Candidiasis of skin and nail

# Master fungal skin vector
fungal_skin <- c(dermatophytoses, other_cutaneous_mycoses, candidiasis_skin)


# ----------------------------
# Parasitic & ectoparasitic infections affecting skin & mucous membranes
# ----------------------------
# Scabies and pediculosis (lice)
ectoparasites <- c("B86", "B85.0", "B85.1", "B85.8", "B85.9")

# Cutaneous leishmaniasis / other parasitic skin diseases
parasitic_skin <- c("B55.1", "B55.9", "B80")  # B55.* = leishmaniasis (cutaneous included); B80 included as example helminthic skin presentation

# Master parasitic skin vector
parasitic_ectoparasitic_skin <- c(ectoparasites, parasitic_skin)
```

	# ----------
	# Soft tissue / mixed infections & sequelae (common skin-related codes)
	# ----------
	# Pressure ulcer infected/infected skin ulcer / chronic ulcer with infection are often coded in L89 / L97 with infection flags-include broad L89/L97 references
	pressure_ulcer_infected <- c("L89.0", "L89.1", "L89.2", "L89.3", "L89.4", "L89.5", "L89.6", "L89.7", "L89.8", "L89.9")
	chronic_skin_ulcers_infected <- c("L97.101", "L97.102", "L97.109") # example subcodes; expand as needed per site/severity
	
	# ----------
	# Mucous membrane specific infections (oral, ocular, genital mucosa)
	# ----------
	# Oral mucosa / stomatitis (viral & fungal causes — herpes / candidiasis)
	oral_mucosa_infections <- c("K12.0", "K12.1", "K12.2", "K12.3", "B00.1", "B37.0")
	# (K12 series are stomatitis codes — used for mucosal lesions; B00.1 = herpetic gingivostomatitis; B37.0 = candidal stomatitis)
	
	# Conjunctival / ocular mucous membrane infections (grouped)
	ocular_mucous_infections <- c("H10.0", "H10.1", "H10.2", "H10.3", "H10.4") # conjunctivitis/keratoconjunctivitis group

Bloodstream / systemic infections / sepsis	# ----------
	# Bacterial sepsis & septicemia (A40–A41)
	# ----------
	
	# Streptococcal sepsis
	streptococcal_sepsis <- c("A40.0", "A40.1", "A40.2", "A40.3", "A40.8", "A40.9")
	
	# Staphylococcal sepsis
	staphylococcal_sepsis <- c("A41.0", "A41.1", "A41.2", "A41.3", "A41.4", "A41.5", "A41.8", "A41.9")
	
	# Other bacterial sepsis
	other_bacterial_sepsis <- c("A02.1", "A22.7", "A32.7", "A39.2", "A39.4", "A42.7", "A54.8", "A55.8", "A56.8", "A58.8", "A60.8", "A70.8", "A78.8", "A87.2")
	# Note: A02.1 (Salmonella septicemia) is included as bloodstream; others represent sepsis due to specific bacteria classified elsewhere

```
# Sepsis unspecified
sepsis_unspecified <- c("R65.20", "R65.21")  # R65.20 = severe sepsis w/o septic shock, R65.21 = w/ septic shock

# ----------------------------
# Bacteremia (bloodstream infection, not sepsis)
# ----------------------------
bacteremia <- c("R78.81")  # Bacteremia, unspecified

# ----------------------------
# Fungal systemic infections (bloodstream / disseminated)
# ----------------------------
# Systemic candidiasis (excluding skin/GI/resp codes already assigned)
systemic_candidiasis <- c("B37.7")  # Candidal sepsis

# Aspergillosis, systemic
systemic_aspergillosis <- c("B44.7")  # Disseminated aspergillosis (bloodstream/systemic)

# Cryptococcosis, systemic
systemic_cryptococcosis <- c("B45.1")  # Cerebral previously assigned to CNS; B45.2–B45.9 = other systemic involvement

# Other systemic mycoses
systemic_other_fungal <- c("B46.1", "B48.2")  # mucormycosis/mycotic infection, disseminated

# ----------------------------
# Viral systemic infections
# ----------------------------
# Viremia / systemic viral infections (exclude organ-specific CNS/resp/GI)
systemic_viral <- c("B33.0", "B33.1", "B33.2", "B33.8", "B34.2", "B34.8")
# Note: B33.* = viral infections of unspecified sites; B34.* = viral infection of unspecified site

# ----------------------------
# Parasitic systemic infections
# ----------------------------
```

	systemic_parasitic <- c("B50.0", # Cerebral malaria already in CNS, other malaria here "B50.8", "B51.0", "B51.8", "B52.0", "B52.8", "B53.0", "B53.8", "B54") # Systemic malaria (excluding CNS), other systemic protozoal infections # ---------- # Bloodstream infections secondary to other bacteria classified elsewhere # ---------- bloodstream_other <- c("B95.0","B95.1","B95.2","B95.3","B95.4","B95.5","B95.6","B95.7","B96.0","B96.1","B96.20","B96.29") # Note: used B95/B96 in respiratory or GI only when organ-specific; here systemic/bloodstream general sepsis use

Cardiac / endovascular infections	# ----------
	# Infective endocarditis (I33, I38, I39)
	# ----------
	
	# Acute and subacute infective endocarditis
	endocarditis <- c("I33.0", "I33.9") # I33.0 = acute, I33.9 = unspecified endocarditis
	
	# Endocarditis due to underlying heart valve disease
	endocarditis_valve <- c("I38") # Endocarditis valve unspecified
	
	# Endocarditis in bacterial diseases classified elsewhere
	endocarditis_bacterial_elsewhere <- c("I39") # I39 = endocarditis in bacterial diseases classified elsewhere
	
	# ----------
	# Myocarditis of infectious origin (I40)
	# ----------
	# Acute myocarditis
	myocarditis <- c("I40.0", "I40.1", "I40.8", "I40.9")
	
	# ----------
	# Pericarditis of infectious origin (I30)
	# ----------
	# Acute pericarditis, infectious
	pericarditis <- c("I30.0", "I30.8", "I30.9") # Excludes post-surgical/post-MI

	# ----------
	# Septic emboli / endovascular infections (arterial, venous, systemic with cardiac focus)
	# ----------
	endovascular_sepsis <- c("I74.0", "I74.1", "I74.2", "I74.3", "I74.4", "I74.5", "I74.8", "I74.9")
	# I74 = arterial embolism/thrombosis; if infectious, can reflect endovascular source
	
	# Bacterial infections of cardiac devices (ICD-10 T82.6xx)
	cardiac_device_infection <- c("T82.60", "T82.61", "T82.62", "T82.63", "T82.64", "T82.65", "T82.66", "T82.67", "T82.68", "T82.69")
	# T82.6 = infection/ inflammatory reaction due to cardiac device, implant, or graft
	
	# ----------
	# Fungal endocarditis / cardiac fungal infections (B37, B44)
	# ----------
	# Systemic fungal infections involving heart
	fungal_endocarditis <- c("B37.6", "B44.7")
	# Note: B37.6 = candidal encephalitis previously excluded; here including systemic/endocardial involvement only if not assigned to CNS or bloodstream
	
	# ----------
	# Viral myocarditis/pericarditis (B33 series)
	# ----------
	viral_cardiac_infections <- c("B33.2", "B33.8")
	# B33.2 = viral myocarditis, B33.8 = other viral infections of heart/muscle

Genitourinary	# ----------
	#Genitourinary infections
	# ----------
	
	# Acute and other cystitis
	cystitis <- c("N30.0","N30.00","N30.01","N30.1","N30.20","N30.21","N30.8","N30.9")
	
	# Asymptomatic bacteriuria
	asymptomatic_bacteriuria_nonpregnant <- c("R82.71")

```
# Asymptomatic bacteriuria in pregnancy / urinary tract infection in pregnancy
asymptomatic_bacteriuria_pregnant <- c("O23.0","O23.5","O23.9")

# Acute urethritis
urethritis <- c("N34.0","N34.1","N34.2","N34.3","N34.8","N34.9")

# Pyelonephritis (kidney infections)
pyelonephritis <- c("N10","N11.0","N11.1","N11.8","N12","N13.6")

# Prostatitis
prostatitis <- c("N41.0","N41.1","N41.8","N41.9")

# Gonococcal urethritis
gonococcal_urethritis <- c("A54.0","A54.1","A54.2","A54.3","A54.41","A54.42","A54.49")

# Chlamydial urethritis / prostatitis
chlamydial_urethritis <- c("A56.0","A56.1","A56.2","A56.3","A56.8","A56.9")

# Other bacterial urinary infections
other_bacterial_urinary <- c("N39.0","N39.8")

# Fungal genitourinary infections
candidiasis_urinary <- c("B37.3")  # Candidiasis of genitourinary tract

# Viral genitourinary infections
viral_urinary <- c("B00.5","B25.8")  # HSV or CMV

# Parasitic / protozoal infections
trichomoniasis <- c("A59.0","A59.8","A59.9")  # Trichomoniasis

# Other urinary/genitourinary bacterial infections not elsewhere specified
other_urinary_infections <- c("N39.1","N39.9")  # Urinary tract infections site unspecified / other
```

	# Infections related to urinary catheters or instrumentation
	catheter_related_infections <- c("T83.511A","T83.519A","T83.521A","T83.529A") # Infection of urinary device

Reproductive Tract, Sexually Transmitted and Blood Borne Infections	# ----------
	# Reproductive tract and sexually transmitted infections (STIs)
	# ----------
	
	# Gonococcal infections
	gonococcal <- c("A54.0","A54.1","A54.2","A54.3","A54.41","A54.42","A54.49") # Urethritis, cervicitis, gonococcal infections
	
	# Chlamydial infections
	chlamydial <- c("A56.0","A56.1","A56.2","A56.3","A56.8","A56.9") # Urethritis, cervicitis, prostatitis
	
	# Syphilis
	syphilis <- c("A50.0","A50.1","A50.2","A50.3","A50.4","A50.5","A50.6","A50.7","A50.8","A50.9",
	"A51.0","A51.1","A51.2","A51.3","A51.4","A51.5","A51.8","A51.9",
	"A52.0","A52.1","A52.2","A52.3","A52.7","A52.8","A52.9",
	"A53.0","A53.1","A53.2","A53.8","A53.9") # Congenital & acquired syphilis
	
	# Trichomoniasis
	trichomoniasis <- c("A59.0","A59.8","A59.9")
	
	# Human papillomavirus (HPV)
	hpv <- c("A63.0","B97.7") # Genital HPV infection / HPV as cause of diseases
	
	# Herpes simplex virus (genital)
	herpes_genital <- c("A60.0","A60.1","A60.2","A60.8","A60.9","B00.5") # Genital HSV infections
	
	# HIV
	hiv <- c("B20","B21","B22","B24") # HIV disease, various manifestations
	
	# Hepatitis C virus (HCV)
	hcv <- c("B17.1","B18.2") # Acute and chronic HCV

	# Hepatitis B virus (HBV)
	hbv <- c("B16.0","B16.1","B16.2","B16.9","B18.0","B18.1") # Acute and chronic HBV
	
	# Other sexually transmitted infections
	other_sti <- c("A57","A58","A63.8","A63.9") # Chancroid, lymphogranuloma venereum, other unspecified STIs
	
	# Maternal infections affecting reproductive tract during pregnancy
	sti_pregnancy <- c("O98.0","O98.1","O98.2","O98.3","O98.4","O98.5","O98.8","O98.9")
	# Infections with potential effect on pregnancy (syphilis, gonorrhea, chlamydia, HIV)

Bone / joint / soft tissue infections	# ----------
	# Bone, joint, and soft tissue infections
	# ----------
	
	# Osteomyelitis (bone infections)
	osteomyelitis <- c(
	  "M86.0","M86.1","M86.2","M86.3","M86.4","M86.5","M86.6","M86.8","M86.9"
	)
	# Acute, chronic, hematogenous, unspecified
	
	# Septic arthritis (joint infections)
	septic_arthritis <- c(
	  "M00.0","M00.1","M00.2","M00.3","M00.8","M00.9"
	)
	# Staphylococcal, streptococcal, other bacteria, unspecified
	
	# Infectious bursitis / tendon sheath infections
	bursitis_tendon <- c(
	  "M65.0","M65.1","M65.2","M65.3","M65.8","M65.9"
	)
	# Infectious synovitis/tendonitis
	
	# Soft tissue abscesses, cellulitis, pyomyositis (excluding skin codes already assigned)

	soft_tissue_infections <- c(
	  "M72.6","M72.7","M72.8","M72.9",
	  "M79.0","M79.1","M79.2","M79.8","M79.9"
	)
	# Myositis, pyomyositis, deep soft tissue abscesses
	
	# Prosthetic joint infections (device-related)
	prosthetic_joint_infection <- c(
	  "T84.50XA","T84.51XA","T84.52XA","T84.59XA"
	)
	# Infection/inflammatory reaction due to prosthetic joint
	
	# Bone infections due to tuberculosis
	tb_bone <- c(
	  "A18.0","A18.1","A18.2","A18.3","A18.4","A18.5"
	)
	# Tuberculosis of bones and joints
	
	# Other bacterial bone/joint infections
	other_bacterial_bone <- c(
	  "A32.6","A39.5","A42.0","A42.1","A42.2","A42.7"
	)
	# Actinomycosis, meningococcal arthritis, corynebacterial osteomyelitis, other bacterial

Vector-borne / arthropod-borne diseases	# ----------
	# Vector-borne and Arthropod-borne Diseases
	# ----------
	
	# Malaria
	malaria <- c("B50.0","B50.1","B50.8","B50.9",
	  "B51.0","B51.1","B51.8","B51.9",
	  "B52.0","B52.1","B52.8","B52.9",
	  "B53.0","B53.8","B54")

	# Dengue
	dengue <- c("A90","A91")
	
	# Yellow fever
	yellow_fever <- c("A95")
	
	# Chikungunya
	chikungunya <- c("A92.0")
	
	# Zika virus infection
	zika <- c("A92.5")
	
	# Other mosquito-borne viral fevers
	other_mosquito_viral <- c("A92.8","A92.9")
	
	# Tick-borne bacterial infections
	lyme_disease <- c("A69.2") # Lyme disease
	rickettsial_infections <- c("A77","A78","A79.0","A79.8","A79.9") # Spotted fever, Q fever, typhus
	
	# Tick-borne viral infections
	tick_borne_viral <- c("A84.0","A84.1","A84.2","A84.3","A84.8","A84.9") # Tick-borne encephalitis
	
	# Flea-borne infections
	plague <- c("A20.0","A20.1","A20.2","A20.3","A20.7","A20.8","A20.9")
	
	# Sandfly / other arthropod-borne infections
	leishmaniasis <- c("B55.0","B55.1","B55.2","B55.9") # Cutaneous, mucocutaneous, visceral
	
	# Other specified arthropod-borne viral fevers
	other_arboviral <- c("A92.3","A92.4","A92.8","A92.9") # Including hemorrhagic fever, other specified

Protozoal / parasitic systemic diseases	# ---------- # Protozoal and Parasitic Infections # ----------

```
# Intestinal protozoal infections (non-GI ones already in GI vector are excluded)
extraintestinal_amebiasis <- c("B58.0","B58.1") # Tissue amebiasis, extraintestinal
toxoplasmosis <- c("B58.0","B58.1","B58.8","B58.9") # Includes CNS or ocular if not captured elsewhere

# Malaria (also vector-borne, included here for completeness if needed)
malaria_parasitic <- c("B50.0","B50.1","B50.8","B50.9",
                       "B51.0","B51.1","B51.8","B51.9",
                       "B52.0","B52.1","B52.8","B52.9",
                       "B53.0","B53.8","B54")

# Trypanosomiasis
african_trypanosomiasis <- c("B56.0","B56.1","B56.2","B56.3","B56.8","B56.9") # African trypanosomiasis, unspecified
american_trypanosomiasis <- c("B57.0","B57.1","B57.2","B57.3","B57.4","B57.5","B57.8","B57.9") # Chagas disease

# Leishmaniasis (already included under vector-borne)
leishmaniasis_parasitic <- c("B55.0","B55.1","B55.2","B55.9") # Cutaneous, mucocutaneous, visceral

# Other protozoal infections
giardiasis <- c("A07.1")  # Giardia intestinalis
cryptosporidiosis <- c("A07.2")  # Cryptosporidium infection (extraintestinal)
isospora <- c("A07.8")  # Other specified protozoal intestinal disease
cyclospora <- c("A07.9")  # Protozoal infection, unspecified

# Helminthic infections (outside GI)
ascariasis <- c("B77")  # Roundworm
enterobiasis <- c("B80")  # Pinworm
hookworm <- c("B81.0")  # Anisakiasis (if extraintestinal)
schistosomiasis <- c("B65.0","B65.1","B65.2","B65.8","B65.9")
filariasis <- c("B74","B74.0","B74.1","B74.8","B74.9")
taeniasis <- c("B68")  # Tapeworm infections
other_helminths <- c("B83.0","B83.1","B83.2","B83.3","B83.4","B83.8","B83.9")
```

Infestations (lice, mites)	Pediculosis_acariasis_other_infestations <- c("B86","B88.9", "B89")
Other / unspecified infectious diseases	Infection_Other <-c ("B33.2, I43.0", "B34.9", "B99", "T82.701, Y83.1", "A49.8", "H66.9", "H60.3", "B00.9", "A49.9, U83.7", "A04.0", "A04.1", "A04.2", "A04.3", "A04.4", "A04.5", "A04.6", "A04.8", "I40.0", "A49.9, U83.7") #Viral cardiomyopathy, myocarditis, Viral unspecified, infection unspecified, bloodstream infection due to port-a-cath, ESBL producing Klebsiella identified source unspecified, H. Pylori(unspecified), internal/external ear infection, HSV-2, gastrointestinal unspecified Fever_Unknown_Origin <- c("R50.9") Viral_Exanthem <-c ("B09")

Appendix R: Multivariable Logistic Regression Model with Antibiotic Prescribing as Outcome Variable and Effect Modification by Sex Assessed

Covariate	Odds Ratio	CI (low)	CI (high)	p value
(Intercept)	0.10	0.09	0.11	-
Female sex (reference male)	0.74	0.68	0.81	<0.001
PAL presence (reference PAL absent)	1.43	1.15	1.77	<0.001
65-80 years (reference <65 years)	1.40	1.28	1.53	<0.001
>80 years (reference <65 years)	1.97	1.76	2.19	<0.001
2 allergy labels (reference 0-1 allergy label)	1.05	0.90	1.23	0.51
3+ allergy labels (reference 0-1 allergy label)	1.18	0.99	1.41	0.06
Atopic conditions (no reference category)	1.20	1.05	1.37	<0.01
Autoimmune inflammatory conditions (no reference category)	1.14	0.97	1.35	0.11
Metabolic condition (obesity) (no reference category)	1.44	1.09	1.87	<0.01
Chronic obstructive pulmonary disease (no reference category)	1.88	1.59	2.21	<0.001
Interaction term: Female*PAL (Reference Male* PAL absent)	0.81	0.63	1.06	0.12

Legend: CI- Confidence Interval; PAL- Penicillin Allergy Label

Appendix S: Multivariable Logistic Regression Model with Antibiotic Prescribing as Outcome Variable

Covariate	Odds Ratio	CI (low)	CI (high)	p value
(Intercept)	0.10	0.09	0.11	-
Female sex (reference male)	0.73	0.67	0.79	<0.001
PAL presence (reference PAL absent)	1.25	1.09	1.43	<0.001
65-80 years (reference <65 years)	1.40	1.28	1.53	<0.001
>80 years (reference <65 years)	1.97	1.76	2.19	<0.001
2 allergy labels (reference 0-1 allergy label)	1.06	0.90	1.24	0.50
3+ allergy labels (reference 0-1 allergy label)	1.17	0.98	1.39	0.09
Atopic conditions (no reference category)	1.20	1.05	1.37	<0.01
Autoimmune inflammatory conditions (no reference category)	1.14	0.96	1.35	0.12
Metabolic condition (obesity) (no reference category)	1.44	1.09	1.87	<0.01
Chronic obstructive pulmonary disease (no reference category)	1.88	1.59	2.21	<0.001

Legend: CI- Confidence Interval; PAL- Penicillin Allergy Label

Appendix T: Firth's Adjusted Multivariable Logistic Regression Models with Class Utilization as Outcome Variable (No Effect Modification)

Outcome	Variable	Odds Ratio	CI (low)	CI (high)	p-value
Penicillins	**(Intercept)**	0.03	0.03	0.03	-
	Female sex (reference male)	0.73	0.63	0.83	**<0.001**
	PAL presence (reference PAL absent)	0.33	0.23	0.48	**<0.001**
	65-80 years (reference <65 years)	1.55	1.33	1.80	**<0.001**
	>80 years (reference <65 years)	2.01	1.66	2.43	**<0.001**
	2 allergy labels (reference 0-1 allergy label)	1.01	0.74	1.36	0.96
	3+ allergy labels (reference 0-1 allergy label)	1.12	0.80	1.57	0.52
	Atopic conditions (no reference category)	1.36	1.09	1.70	**<0.01**
	Autoimmune inflammatory conditions (no reference category)	1.14	0.85	1.53	0.38
	Metabolic condition (obesity) (no reference category)	1.43	0.91	2.26	0.12
	Chronic obstructive pulmonary disease (no reference category)	2.18	1.69	2.82	**<0.001**
Cephalosporins	**(Intercept)**	0.02	0.02	0.03	-
	Female sex (reference male)	0.66	0.56	0.77	**<0.001**
	PAL presence (reference PAL absent)	1.08	0.82	1.43	0.59
	65-80 years (reference <65 years)	1.46	1.22	1.75	**<0.001**
	>80 years (reference <65 years)	2.23	1.81	2.76	**<0.001**
	2 allergy labels (reference 0-1 allergy label)	1.13	0.83	1.55	0.44
	3+ allergy labels (reference 0-1 allergy label)	1.00	0.68	1.45	0.98
	Atopic conditions (no reference category)	1.17	0.90	1.53	0.24
	Autoimmune inflammatory conditions (no reference category)	1.01	0.71	1.44	0.96
	Metabolic condition (obesity) (no reference category)	2.32	1.51	3.58	**<0.001**
	Chronic obstructive pulmonary disease (no reference category)	1.18	0.83	1.69	0.36
Carbapenems	**(Intercept)**	0.00	0.00	0.00	-
	Female sex (reference male)	0.57	0.30	1.08	0.08
	PAL presence (reference PAL absent)	1.96	0.80	4.79	0.14

	65-80 years (reference <65 years)	2.73	1.35	5.53	**<0.01**
	>80 years (reference <65 years)	2.92	1.23	6.96	**<0.05**
	2 allergy labels (reference 0-1 allergy label)	1.64	0.59	4.55	0.34
	3+ allergy labels (reference 0-1 allergy label)	1.09	0.29	4.06	0.90
	Atopic conditions (no reference category)	1.11	0.39	3.12	0.85
	Autoimmune inflammatory conditions (no reference category)	1.37	0.41	4.59	0.61
	Metabolic condition (obesity) (no reference category)	0.82	0.06	10.98	0.88
	Chronic obstructive pulmonary disease (no reference category)	2.65	1.02	6.87	**<0.05**
Macrolides	**(Intercept)**	0.00	0.00	0.01	-
	Female sex (reference male)	0.99	0.72	1.36	0.93
	PAL presence (reference PAL absent)	2.94	1.96	4.40	**<0.001**
	65-80 years (reference <65 years)	1.02	0.72	1.46	0.90
	>80 years (reference <65 years)	0.72	0.42	1.24	0.24
	2 allergy labels (reference 0-1 allergy label)	0.80	0.45	1.42	0.45
	3+ allergy labels (reference 0-1 allergy label)	0.68	0.36	1.29	0.24
	Atopic conditions (no reference category)	2.26	1.53	3.35	**<0.001**
	Autoimmune inflammatory conditions (no reference category)	1.42	0.81	2.49	0.22
	Metabolic condition (obesity) (no reference category)	0.68	0.20	2.37	0.55
	Chronic obstructive pulmonary disease (no reference category)	5.08	3.24	7.97	**<0.001**
Fluoroquinolones	**(Intercept)**	0.02	0.01	0.02	-
	Female sex (reference male)	0.69	0.57	0.82	**<0.001**
	PAL presence (reference PAL absent)	2.54	1.96	3.28	**<0.001**
	65-80 years (reference <65 years)	1.28	1.03	1.58	**<0.05**
	>80 years (reference <65 years)	2.06	1.61	2.62	**<0.001**
	2 allergy labels (reference 0-1 allergy label)	0.93	0.65	1.33	0.70
	3+ allergy labels (reference 0-1 allergy label)	0.98	0.66	1.45	0.92
	Atopic conditions (no reference category)	0.74	0.52	1.06	0.10

	Autoimmune inflammatory conditions (no reference category)	0.89	0.58	1.36	0.58
	Metabolic condition (obesity) (no reference category)	1.25	0.65	2.40	0.49
	Chronic obstructive pulmonary disease (no reference category)	1.89	1.33	2.70	**<0.001**
Tetracyclines	**(Intercept)**	0.01	0.00	0.01	-
	Female sex (reference male)	0.74	0.53	1.05	0.09
	PAL presence (reference PAL absent)	1.66	1.02	2.69	**<0.05**
	65-80 years (reference <65 years)	0.68	0.44	1.03	0.07
	>80 years (reference <65 years)	0.65	0.35	1.19	0.17
	2 allergy labels (reference 0-1 allergy label)	1.62	0.90	2.89	0.11
	3+ allergy labels (reference 0-1 allergy label)	2.56	1.46	4.51	**<0.01**
	Atopic conditions (no reference category)	1.27	0.77	2.11	0.35
	Autoimmune inflammatory conditions (no reference category)	1.81	1.05	3.14	**<0.05**
	Metabolic condition (obesity) (no reference category)	1.31	0.46	3.74	0.62
	Chronic obstructive pulmonary disease (no reference category)	1.13	0.48	2.66	0.78
Topical Agents	**(Intercept)**	0.00	0.00	0.00	-
	Female sex (reference male)	0.95	0.63	1.43	0.79
	PAL presence (reference PAL absent)	1.07	0.57	2.01	0.84
	65-80 years (reference <65 years)	2.76	1.73	4.38	**<0.001**
	>80 years (reference <65 years)	5.02	3.05	8.26	**<0.001**
	2 allergy labels (reference 0-1 allergy label)	1.31	0.63	2.72	0.47
	3+ allergy labels (reference 0-1 allergy label)	2.12	1.07	4.20	**<0.05**
	Atopic conditions (no reference category)	1.64	0.92	2.91	0.09
	Autoimmune inflammatory conditions (no reference category)	0.99	0.43	2.31	0.99
	Metabolic condition (obesity) (no reference category)	3.23	1.26	8.23	**<0.05**
	Chronic obstructive pulmonary disease (no reference category)	0.60	0.21	1.71	0.34
Aminoglycosides	**(Intercept)**	0.00	0.00	0.00	-
	Female sex (reference male)	1.37	0.43	4.32	0.59

	PAL presence (reference PAL absent)	1.62	0.46	5.69	0.45
	65-80 years (reference <65 years)	3.01	0.90	10.09	0.07
	>80 years (reference <65 years)	4.28	1.12	16.34	**<0.05**
	2 allergy labels (reference 0-1 allergy label)	0.60	0.05	7.17	0.69
	3+ allergy labels (reference 0-1 allergy label)	5.19	1.48	18.21	**<0.05**
	Atopic conditions (no reference category)	1.66	0.49	5.67	0.42
	Autoimmune inflammatory conditions (no reference category)	1.70	0.38	7.54	0.49
	Metabolic condition (obesity) (no reference category)	1.87	0.16	21.60	0.61
	Chronic obstructive pulmonary disease (no reference category)	6.17	2.00	19.02	**<0.01**
Lincosamides and Glycopeptides	**(Intercept)**	0.00	0.00	0.00	-
	Female sex (reference male)	0.67	0.44	1.04	0.07
	PAL presence (reference PAL absent)	4.50	2.69	7.54	**<0.001**
	65-80 years (reference <65 years)	0.83	0.49	1.39	0.48
	>80 years (reference <65 years)	1.08	0.56	2.06	0.83
	2 allergy labels (reference 0-1 allergy label)	1.52	0.80	2.88	0.20
	3+ allergy labels (reference 0-1 allergy label)	0.71	0.29	1.79	0.47
	Atopic conditions (no reference category)	1.04	0.52	2.09	0.91
	Autoimmune inflammatory conditions (no reference category)	2.14	1.09	4.17	**<0.05**
	Metabolic condition (obesity) (no reference category)	1.02	0.21	4.92	0.98
	Chronic obstructive pulmonary disease (no reference category)	0.76	0.22	2.62	0.67
Folate Synthesis Inhibitors	**(Intercept)**	0.01	0.01	0.01	-
	Female sex (reference male)	0.53	0.38	0.73	**<0.001**
	PAL presence (reference PAL absent)	0.91	0.51	1.61	0.74
	65-80 years (reference <65 years)	0.94	0.64	1.37	0.73
	>80 years (reference <65 years)	1.17	0.72	1.90	0.52
	2 allergy labels (reference 0-1 allergy label)	1.03	0.51	2.09	0.94
	3+ allergy labels (reference 0-1 allergy label)	2.59	1.44	4.64	**<0.01**

	Atopic conditions (no reference category)	1.09	0.63	1.87	0.76
	Autoimmune inflammatory conditions (no reference category)	1.48	0.81	2.71	0.20
	Metabolic condition (obesity) (no reference category)	1.38	0.48	3.94	0.55
	Chronic obstructive pulmonary disease (no reference category)	0.91	0.39	2.12	0.82
Other Antibiotic Classes	**(Intercept)**	0.00	0.00	0.00	-
	Female sex (reference male)	1.82	1.32	2.52	**<0.001**
	PAL presence (reference PAL absent)	1.24	0.77	1.99	0.38
	65-80 years (reference <65 years)	1.48	1.07	2.06	**<0.05**
	>80 years (reference <65 years)	1.71	1.13	2.58	**<0.05**
	2 allergy labels (reference 0-1 allergy label)	1.04	0.59	1.82	0.90
	3+ allergy labels (reference 0-1 allergy label)	1.08	0.58	2.00	0.82
	Atopic conditions (no reference category)	0.78	0.45	1.35	0.37
	Autoimmune inflammatory conditions (no reference category)	1.00	0.54	1.86	1.00
	Metabolic condition (obesity) (no reference category)	0.51	0.10	2.47	0.40
	Chronic obstructive pulmonary disease (no reference category)	1.31	0.66	2.63	0.44

Legend: CI- Confidence Interval; PAL- Penicillin Allergy Label

Appendix U: Multivariable Logistic Regression Model with Guideline Concordant Beta-Lactam Utilization as Outcome Variable

Covariate	Odds Ratio	CI (low)	CI (high)	p value
(Intercept)	1.51	0.89	2.55	-
Female sex (reference male)	0.89	0.44	1.80	0.75
PAL presence (reference PAL absent)	0.46	0.14	1.55	0.21
65-80 years (reference <65 years)	0.91	0.42	1.95	0.80
>80 years (reference <65 years)	0.79	0.28	2.26	0.66
2 allergy labels (reference 0-1 allergy label)	0.83	0.24	2.84	0.76
3+ allergy labels (reference 0-1 allergy label)	0.72	0.15	3.33	0.67
Atopic conditions (no reference category)	0.75	0.25	2.21	0.60
Autoimmune inflammatory conditions (no reference category)	1.48	0.37	5.96	0.58
Metabolic condition (obesity) (no reference category)	5.99	0.20	181.33	0.30
Chronic obstructive pulmonary disease (no reference category)	0.74	0.14	3.92	0.72

Legend: CI- Confidence Interval; PAL- Penicillin Allergy Label