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Original Article

The Burden of Self-Reported Antibiotic Allergies in Health Care and How to Address It: A Systematic Review of the Evidence

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What is already known about this topic? Allergy to beta-lactam antibiotics is the most reported medication allergy and a substantial growing public health concern. Approximately 10% to 15% of the adult population internationally has reported allergies to beta-lactams, the most used antimicrobial class.

What does this article add to our knowledge? Unverified antibiotic allergy labels are associated with poorer patient clinical outcomes. Systematic antibiotic allergy assessment services can be established, which have been shown to improve patient care for adults and children globally.

How does this study impact current management guidelines? There is variability globally in the current assessment of antibiotic allergy. This review highlights the need to delabel antibiotic allergy in a standardized, safe, accurate, and cost-effective manner, to optimize patient care.

BACKGROUND: Antibiotics are the first-line treatment for bacterial infections; however, overuse and inappropriate prescribing have made antibiotics less effective with increased antimicrobial resistance. Unconfirmed reported antibiotic allergy labels create a significant barrier to optimal antimicrobial stewardship in health care, with clinical and economic implications.

OBJECTIVE: A systematic review was conducted to summarize the impact of patient-reported antibiotic allergy on clinical outcomes and various strategies that have been employed to effectively assess and remove these allergy labels, improving patient care.

METHODS: The review was undertaken using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A critical appraisal was conducted on all studies and a narrative synthesis was performed to identify themes.

RESULTS: Four themes emerged: the prevalence of antibiotic allergy, impact of antibiotic allergy on antimicrobial prescribing, impact of antibiotic allergy on clinical outcomes, and delabeling strategies to improve clinical outcomes. Of the 32 studies, including 1,089,675 participants, the prevalence of reported antibiotic allergy was between 5% and 35%. Patients with a reported antibiotic allergy had poorer concordance with prescribing guidelines in 30% to 60% of cases, with a higher use of alternatives such as quinolone, tetracycline, macrolide, lincosamide, and carbapenem and lower use of beta-lactam antibiotics. Antibiotic allergy delabeling was identified as an intervention and recommendation to advance the state of the science.

CONCLUSIONS: There is substantial evidence within the literature that antibiotic allergy labels significantly impact patient clinical outcomes and a consensus that systematic assessment of reported antibiotic allergies, commonly referred to as delabeling, improves the clinical management of patients. **(J Allergy Clin Immunol Pract 2023;11:3133-45)**

Key words: *Antibiotic allergy; Delabeling; Antimicrobial stewardship; Drug allergy*

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Abbreviations used
AALs- Antibiotic allergy labels
AMS- Antimicrobial stewardship
JBI- Joanna Briggs Institute
MRSA- Methicillin-resistant Staphylococcus aureus
NAALs- No antibiotic allergy labels

INTRODUCTION

Antimicrobial resistance is increasing while antimicrobial drug development is decreasing; therefore, antimicrobial stewardship (AMS) is paramount in optimizing the use of antimicrobials, preventing the development of antibiotic resistance, and improving patient outcomes.[1] Allergy to penicillins accounts for the most common reported medication allergy and is a substantial and growing public health concern.[2] Approximately 10% to 15% of the adult population internationally has reported antibiotic allergy labels (AALs) to penicillins, the most used antimicrobial class. However, up to 90% of patients with a reported penicillin allergy are not allergic and evidence shows that this label is related to adverse patient outcomes.[2-6] Many patients lack a detailed knowledge of their allergy, type of antibiotic, or allergic reaction. This, combined with a lack of understanding amongst health care providers, especially in terms of cross reactivity between beta-lactam antibiotics, leads to broader or suboptimal antibiotic use.[2]

The denial of first-line antibiotics has increased the use of alternative more broad-spectrum antibiotics (such as vancomycin, quinolones, or macrolides), which are linked to the development of infections with antibiotic-resistant organisms[7] such as vancomycin-resistant *Enterococcus*, methicillin-resistant *Staphylococcus aureus* (MRSA), and *Clostridium difficile*.[7-9]

Reported antibiotic allergy in children is also increasing,[10] the majority having an AAL against a beta-lactam antibiotic.[10,11] Within pediatrics, the rate of antibiotic use and resistance is comparable to adults.[12] In Australia, 6-10% of children presenting to hospital have a reported antibiotic allergy,[13] with over 90% of these reports being inaccurate.[14] Both within the adult and the pediatric population, AALs create a barrier to AMS with clinical and economic implications.[15] Antimicrobial stewardship is an international concept of reducing inappropriate antibiotic use to improve the safe and appropriate use of antibiotics within Australian hospitals.

Whereas other systematic reviews have examined aspects of penicillin allergy management,[16-19] this systematic review examines both the impact of antibiotic allergy, including penicillin and beta-lactam allergy, on patient clinical outcomes, and the current and novel strategies to effectively delabel AAL, from an adult and a pediatric perspective.

METHODS

Inclusion criteria

This literature review was conducted using the Population, Intervention, Comparison, and Outcome (PICO) framework (Table E1; available in this article's Online Repository at www.jaci-inpractice.org).[20] The population of interest identified patients admitted to the hospital with a reported antibiotic allergy including beta-lactam, penicillins, and cephalosporins. The intervention included patients who were admitted under or reviewed by infectious diseases or AMS services, with the comparison being patients admitted to the hospital under the same specialty, with no reported beta-lactam allergy, receiving standard care. The outcome examined the impact of antibiotic allergy on clinical outcomes, such as length of hospital stay, inappropriate prescribing, readmission, and mortality.

Studies that examined the implementation of interventions addressing these impacts on clinical outcomes were also included. There was no exclusion in terms of country of origin, area of specialty, or age of patients.

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 1).[21] The review protocol was prospectively submitted and approved within PROSPERO in February 2021 (review number 159509).

Search strategy

The search strategy aimed to find peer-reviewed articles published in English between 2010 and 2022. This timeframe was to ensure that the most recent evidence-based studies were identified. The initial database search was conducted using Medical Literature Analysis and Retrieval System Online (MEDLINE) and Cumulative Index for Nursing and Allied Health Literature (CINAHL). An analysis was then undertaken of the text words contained in the title and abstract and the index terms used in the description of the article. Once appropriate search terms were identified, the search was then extended using Excerpta Medical Database (EMBASE), The U.S. Library of Medicine (PubMed) and the Cochrane Library. The full search strategy, including search terms, is provided in Figure E1 (available in this article's Online Repository at www.jaci-inpractice.org).

Study selection

Once the database searches had identified articles, duplicates were removed, and articles were limited to those that met the inclusion criteria. Each article was reviewed by 2 of 3 reviewers (A.A., L.L.C., M.J.F.), who independently screened titles and abstracts, excluding studies that did not meet the inclusion criteria. Two reviewers in pairs (A.A., L.L.C., M.J.F.) also did full text screening of articles, with any study that did not meet the inclusion criteria excluded. Identified disagreements were resolved between the reviewers through discussion or with the third reviewer.

Assessment of methodological quality

The selected articles were critically appraised using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Cohort, Case Series and Quasi-experimental studies. Each question was answered with 1 of 4 ratings (yes, no, unclear, or not applicable). Each article was assessed by 2 of 3 reviewers (A.A., L.L.C., M.J.F.) and disagreements were resolved between the reviewers through discussion or with the third reviewer (Table E2; available in this article's Online Repository at www.jaci-inpractice.org).

Data extraction

The studies were divided into those with an intervention and those with without an intervention. Data extracted included the author, title, year of publication, country of publication, the study design, sample type and size, type of intervention, data collected, main results, limitations, and recommendations (Table I).

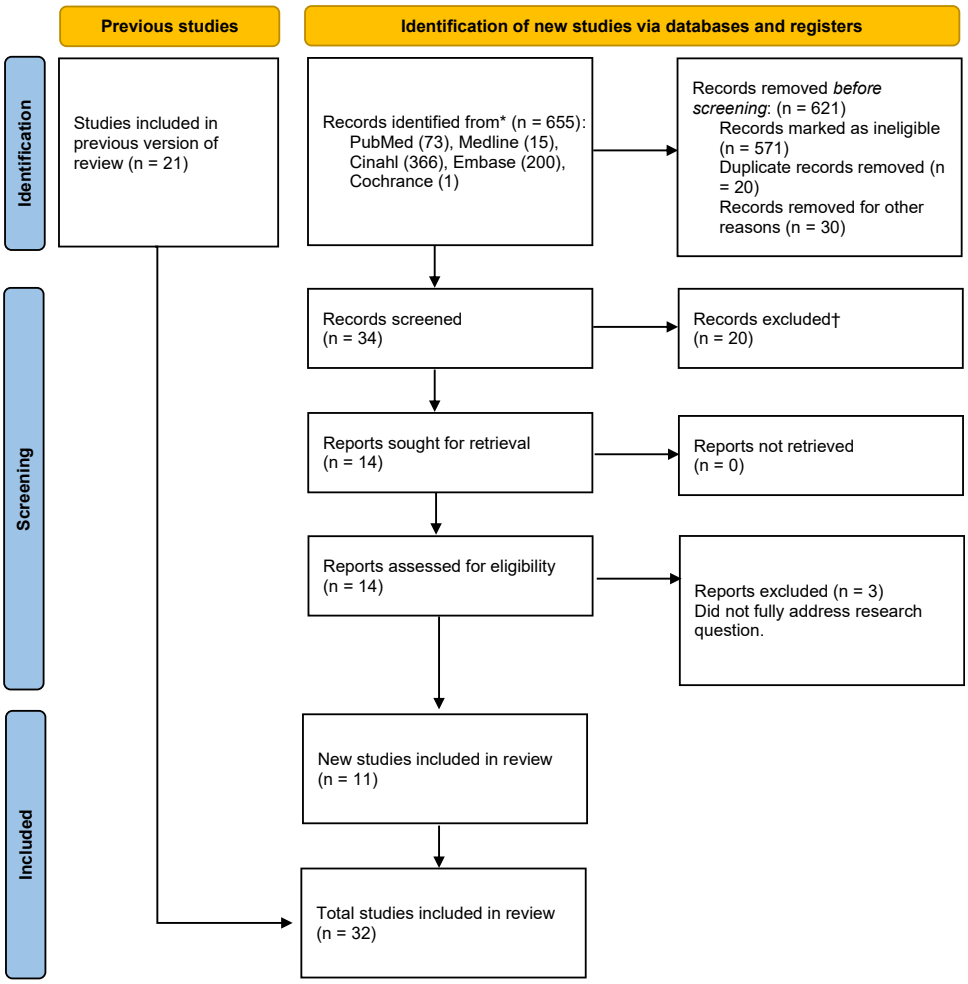

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram for updated systematic reviews that included searches of databases and registers only. (From Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffman TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.) For more information, visit: http://www.prisma-statement.org/.

Owing to heterogeneity of outcome measures, a meta-analysis of quantitative data could not be completed. A narrative synthesis was completed to report the findings.[47]

RESULTS

Two searches were conducted, the first search (up to January 2019) then a second search (January 2019 to April 2022) was performed to update the literature. After duplicates were removed and limiters applied, the first search included 21 articles and the second search included 11 articles. A total of 32 articles were included in this review (Figure 1).

These articles were then assessed by 2 independent viewers (A.A., L. L.C., M.J.F.), for methodological quality, using the JBI Critical Appraisal Tool as represented in Table E2.[48] The overall methodological quality of the included studies was very good with most questions answered positively for the cohort studies, case series, and quasi-experimental studies (Table E2).

The studies included in this review were published from 2015 to 2022, originating from the United States of America,[2,5,26-29,33-35,37,38,40,41] Canada,[6] Australia,[4,22-25,30,31,42-45] New Zealand,[3,32] United Kingdom,[49] Spain,[36] Norway,[39] and the Netherlands[46] (Table I). The studies were cohort studies, case series, and quasi-experimental studies and comprised surveys,[42] retrospective reviews,[2,4,5,22,23,25,28,29,35-38,42-46,49] case series,[25,26,31,32,39] quasi-experimental,[24] and prospective cohort studies.[3,6,27,30,31,33,34,40,41] The total number of participants across the 32 studies was 1,089,675 and the size of the cohorts ranged from 30 to 931,000 patients.

All the studies identified several elements pertaining to the search criteria, and the findings present the 4 themes that emerged from the review. The themes include the prevalence of antibiotic allergy, impact of antibiotic allergy on antimicrobial prescribing, impact of reported antibiotic allergy on clinical outcomes, and delabeling strategies (including risk stratification), as an intervention to improve clinical outcomes. In addition, the studies reported on a range of different factors that were

TABLE I. Data extraction appraisal table

Author, year, and country	Leading team	Study design	Sample size/participants/age	Prevalence/type of reported AAL	Key results	Intervention
Catalano et al (2022)[22] Australia (Melbourne)		Retrospective cohort study	n = 938 children admitted to a tertiary children's hospital Age: 0−18 y	1% Beta-lactam	AAL increased the use of inappropriately prescribed restricted antibiotics. Hospital length of stay was longer for AAL group.	None
Chakravorty et al (2022)[23]Australia (Perth)		Retrospective cohort study	n = 630 referred for antimicrobial prospective audit and feedback rounds. Mean age: 62 y	16% All antibiotics	Patients with AAL were less likely to receive guideline recommended therapy. Higher incidence of developing *C. difficile* or MRSA in AAL group. Drug allergy documentation was generally poor.	None
Chua et al (2021)[24] Australia (Melbourne)	Infectious diseases and immunology	Quasi-experimental study	n = 1,791 acute inpatients identified with a reported antibiotic allergy Median age: 66 y	No prevalence Penicillin	98% (n = 355) of those tested were successfully delabeled. Comparison of antibiotic use prior to and post testing by direct delabeling and oral challenge showed an increase in the use of penicillin antibiotics and lower use of alternative and restricted-use antibiotics.	Direct delabeling or oral provocation challenge
Conway et al (2017)[2] United States (New York)	Infectious diseases	Retrospective cohort study	n = 403 veterans admitted through emergency department at a Veteran Affairs Healthcare Centre Mean age: 75 y	14% Penicillin	AAL leads to delay in administration of antibiotics but does not increase length of stay. Increase in the use of alternative antibiotics in the penicillin-allergic group.	None
du Plessis et al (2019)[3] New Zealand (Auckland)	Pharmacist	Prospective Cohort study	n = 250 admitted to a hospital specializing in infectious diseases and AMS Age: 16−70 y	11% Penicillin	80% of patients with AAL were able to be delabeled by interview alone or oral challenge. 60% had their antimicrobial therapy changed as a result with no adverse events commencing penicillins.	Allergy assessment interview and oral provocation challenge.
Gulholm et al (2021)[25] Australia (New South Wales)	Infectious diseases	Cohort study	n = 844 a convenience sample presenting to emergency department in adult teaching hospital. Age: 16−98 y	10% All antibiotics	30% of those with documented AAL received inappropriate antibiotics. Documentation was poor for AAL group with 1% prescribed their culprit antibiotic.	None
Ham et al (2021)[26] United States (Oregon)		Case series	n = 50 patients admitted to an academic medical center. Age: 21−87 y	12% Penicillin	50 patients underwent a penicillin allergy process. 96% (n = 48) were successfully delabeled. 40% by interview alone and 60% by oral provocation challenge with 1 patient requiring skin testing prior. 54% of these patients had their antibiotic therapy changed as a result.	Direct oral challenge or skin testing ± oral challenge.
Heil et al (2016)[27] United States (Maryland)	Infectious diseases	Prospective cohort study	n = 90 admitted to an academic medical center with reported penicillin allergy. Age not specified	No prevalence Penicillin	90 patients were assessed for PST and 84 patients underwent skin testing. Of the remaining 64 patients, 96% had negative tests. 84% of these had their antibiotic changes to a preferred beta-lactam.	Implementation of infectious disease fellow−led penicillin skin testing service.
Huang et al (2018)[28] United States (Pennsylvania)	Immunology	Retrospective cohort study	n = 4,671 patients with hematological malignancy admitted to 2 tertiary care hospitals Mean Age: 60 y	35% Beta-lactam	Patients with an AAL had a significantly longer length of stay and significantly higher mortality rate at 30 d and 180 d; with a higher readmission rate at 30 d and increased *C. difficile* rate.	None

Jones et al (2021)[29] United States (Utah)	Immunology	Retrospective cohort study	n = 38,906 pediatric patients 30 hospitalized between 2007 and 2017 Age: 1 mo−17 y	9% Beta-lactam	AAL patients were significantly more likely to receive alternative broad-spectrum antibiotics. AAL patients also had higher antimicrobial costs but no differences in costs of hospitalization	None
Knezevic et al (2016)[7] Australia (Western Australia)	Immunology	Retrospective cohort study	n = 775 inpatients captured in the National Antimicrobial Prescribing Survey, 2013 and 2014. Mean age: 62 y	18% All antibiotics	AAL are common but poorly documented. Patients with AAL are significantly more likely to be prescribed alternative antibiotics and have more hospital readmissions.	None
Li et al (2019)[30] Australia (New South Wales)	Immunology and infectious diseases	Prospective cohort study	n = 71 admitted to a tertiary hospital. Median age: 70 y	No prevalence Penicillin	54 (96%) type B reaction patients had negative skin testing and successful 3-d amoxicillin challenge. The study shows that proceeding to oral challenge without skin testing in type B reactions is safe.	Evaluation of penicillin allergy diagnosis. Implementation of direct oral provocation challenge.
Li et al (2021)[31] Australia (New South Wales)	Immunology and infectious diseases	Case series	n = 149 patients enrolled through inpatient and outpatient settings with allergy labels. Age: not specified	No prevalence Penicillin	149 patients received a drug provocation challenge. 43% were considered low risk. 57% were deemed non−low risk. 100% of the low-risk group tolerated the single step, 95% the extended course. 98% in the non−low-risk group tolerated the single step and 94% the extended course.	Single step drug provocation challenge
Livirya et al (2022)[32] New Zealand (Hastings)	Infectious diseases and immunology	Case series	n = 224 patients identified with an active antibiotic allergy record. Mean age: 73 y	16% Penicillin	162 patients were deemed low risk. Of these, 56 had tolerated penicillin antibiotics since the index reaction and were delabeled without challenge together with a further 15 with a nonallergic history. 41 were challenged without issue. Of the original 224 patients screened, 50% were successfully delabeled.	Direct oral provocation challenge.
Lucas et al (2019)[4] Australia (Western Australia)	Immunology	Retrospective cohort study	n = 1,672 patients admitted to a tertiary children's hospital over a 1-y period Age: 0−18 y	5% All antibiotics	Prevalence of antibiotic allergy increased with age. Oncology or other specialties were more likely to have AAL than those in general medical or surgical. AAL significantly increased the use of alternative antimicrobial therapy and increased hospital length of stay.	None
MacFadden et al (2016)[6] Canada (Toronto)	Infectious diseases	Cohort study	n = 507 patients admitted under infectious diseases at 3 academic hospitals. Median age: 59−69 y	19% Beta-lactam	35% of AAL patients did not receive the preferred beta-lactam therapy owing to their reported allergy. These patients are significantly more likely to experience an adverse event.	None
Macy & Shu, (2017)[33] United States (California)		Cohort study	n = 308 matched to 1,251 control patients who were penicillin-allergic attending outpatient services. Median age: 35−39 y	No prevalence Penicillin	Case subjects had significantly fewer outpatient department follow-up visits, hospital days, and emergency department presentation in the 4-y follow-up period than the control patients. They also were prescribed more penicillins and first- and second-generation cephalosporins and less clindamycin and macrolides.	Skin testing followed by direct oral challenge.

(continued)

TABLE I. *(Continued)*

Author, year, and country	Leading team	Study design	Sample size/participants/age	Prevalence/type of reported AAL	Key results	Intervention
Mason et al (2019)[34] United States (New York)		Prospective cohort study	n = 1844 identified through electronic alert, prescribed antibiotics. Mean age: 32 y	12% Beta-lactam	Patients with AAL were significantly less likely to receive the correct drug based on indication and were 2.2 times more likely to receive a fluoroquinolone antibiotic. There was no significant difference in course duration or 30-d readmission/retreatment rates.	None
Modi et al. (2019)[35] United States (Ohio)	Infectious diseases and immunology	Retrospective cohort study	n = 208 patients who had a self-reported beta-lactam allergy and underwent HSCT Median age: 54−57 y	16% pre HSCT 10% post-HSCT Penicillin	Post skin testing and oral challenge an increase in the use of preferred beta-lactam antibiotics and a decrease in the use of alternative antibiotics were noted with a reduced incidence of *C. difficile*. There were not differences in length of stay, intensive care unit admissions, or mortality.	SPT/IDT testing and graded oral challenge.
Perez-Encinas et al (2022)[36] Spain (Madrid)		Retrospective cohort study	n = 931,291 patients discharged from the Spanish hospital system. Median age: 63−70 y	3% Penicillin	Length of hospital stay was significantly higher for those with AAL, however, mortality within this group was lower. Patients with an AAL were significantly older with higher incidence in women, and the penicillin-allergy group had a higher prevalence of infectious diseases.	None
Phan et al (2018)[5] United States (Florida)		Retrospective cohort study	n = 280 patients admitted with a reported penicillin allergy to a community teaching hospital Mean age: 60−65 y	No prevalence Penicillin	The clinical response rate improved in the post-intervention implementation group. There was significantly less use of aztreonam and fluoroquinolone and more frequent use of cephalosporins.	Pharmacy Education Programme. Development of a Penicillin Allergy Guidance Pocket Card.
Powell et al (2022)[19] United Kingdom (Cornwall)		Retrospective cohort study	n = 23,356 inpatients Age: 0−103 y	14% Penicillin	AALs more likely to be female and older and have more comorbidities. They were 4.7 times more likely to receive antibiotics from the non-Access group, those with a higher potential resistance or to be used as a last resort.	None
Seidelman et al (2022)[37] United States (North Carolina)		Retrospective cohort study	n = 39,972 patients undergoing surgery at 3 hospitals between 2013 and 2017. Median Age: 61 years	4% Beta-lactam	Patients with a beta-lactam allergy had 3 times greater odds of developing a surgical site infection that those without.	None
Sigona et al (2016)[38] United States (New York)	Pharmacist	Retrospective cohort study	n = 32 patients admitted with a reported penicillin allergy Median age: 57 y	No prevalence Beta-lactam	32 patients were interviewed, 25% patients post interview were deemed too high risk to change antibiotic therapy. 75% patients had a recommendation to change to a preferred beta-lactam therapy. 87% of these patients received a change in therapy and none had a subsequent hypersensitivity to the antibiotic.	Allergy assessment interview tool

Steenvoorden et al (2021)[39] Norway (Oslo)	General medicine	Case series	n = 257 of patients admitted with a reported penicillin allergy. Mean age: 68−74 y	5% Penicillin	45% of these patients screened met the inclusion criteria for testing, of which 63% were included and tested. Three additional patients were included from other departments. A total of 57 patients were tested. 98% had no immediate reaction to the penicillin and thus had their label removed. 46% of these patients were undergoing antibiotic therapy. 42% of these had their therapy switched to a penicillin immediately after testing.	Direct oral challenge for delabeling hospitalized patients.
Swearingen et al (2016)[40] United States (Pennsylvania)		Cohort study	n = 211 admitted to an academic teaching hospital. Mean age: 65−65 y	No prevalence Penicillin	Post intervention there was a statistically significant decrease in the use an aztreonam post intervention as well as a decrease in the duration of therapy. There was no difference in length of stay or in-hospital mortality between the 2 groups. 83% of patients in the post-intervention group had their aztreonam ceased or changed to an alternative beta-lactam with superior antibiogram susceptibilities.	Restriction of aztreonam/ modification of antibiotic usage in penicillin-allergic patients.
Taremi et al (2019)[41] United States (Texas)	Infectious diseases	Cohort study	n = 100 admitted to a cancer center with a reported penicillin allergy Median age: 65 y	No prevalence Penicillin	95% of patients who underwent skin testing and oral challenge tested negative for penicillin allergy. Skin testing and oral challenge are safe and effective in immunocompromised patients. 51% of these patients had their antibiotic therapy switched to a preferred beta-lactam therapy as a result During follow-up, 56% of those delabeled received beta-lactam therapy and no further reactions were noted.	SPT/IDT testing followed by oral challenge if negative.
Trubiano et al (2015)[42] Australia (Victoria)	Infectious diseases	Prospective cohort study	n = 198 patients admitted to a tertiary cancer unit Median age: 64−65 y	23% All antibiotics	Patient with AAL were found to have a significantly longer duration of therapy. There was no significant difference between the groups in terms of appropriateness of prescribing, but there was a significantly higher use of beta-lactam antibiotics in the nonallergy group	
Trubiano et al (2015)[43] Australia (Victoria)	Infectious diseases	Cohort study	n = 509 patients admitted under AMS. Median age: 58−59 y	25% All antibiotics	The median number of antibiotics used per admission was significant higher and longer in duration for AAL group. There was no difference in mortality or length of stay for each group. There was a significantly higher readmission rate for allergy group.	None

(continued)

TABLE I. *(Continued)*

Author, year, and country	Leading team	Study design	Sample size/participants/age	Prevalence/type of reported AAL	Key results	Intervention
Trubiano et al (2016)[44] Australia (Victoria)	Infectious diseases	Cohort study	n = 21031 patients captured on the NAPS receiving antimicrobials Median age: 66 y	18% All antibiotics	AALs are associated with inappropriate and excess antimicrobial prescribing. A higher proportion of AAL patients had more than 1 noncompliant antimicrobial agent prescribed and the median number of antibiotics prescribed was also higher in this group. For the immunocompromised patients, fluoroquinolones, glycopeptides, and carbapenems were prescribed more in the allergy group.	None
Trubiano et al (2017)[45] Australia (Victoria)	Infectious diseases	Cohort study	n = 118 patients referred to 2 tertiary cancer care units Median age: 59 y	No prevalence Beta-lactam	Evidence that the integration of antibiotic allergy testing into AMS programs enables safe and effective delabeling. 85% of participants had their labels removed. Study reduced restricted antibiotic use and increased use of preferred narrow-spectrum beta-lactam antibiotics.	SPT/IDT plus single-dose oral provocation challenge ± 5 d extended course
Van Dijk et al (2016)[46] Holland		Matched cohort study	n = 17,959 admitted to a Dutch Medical Centre over a 1-y period Median age: 55 y	6% Penicillin	Patients in the allergy group were significantly more likely to receive reserve antibiotics and were more likely to be rehospitalized within 12 wk of admission.	None

HSCT, hematopoietic stem-cell transplantation; *IDT*, intradermal testing; *NAPS*, National Antimicrobial Prescribing Survey; *PST*, penicillin skin testing; *SPT*, skin prick testing.

influenced by the reported AALs in terms of antibiotic prescribing, hospital length of stay, clinician knowledge, and delabeling strategies. The following paragraphs present the findings in relation to these factors.

Prevalence of reported antibiotic allergy

Seventeen studies examined patients with a penicillin allergy label, 8 studies examined patients with a beta-lactam allergy label, the remaining 7 studies reported on all antibiotic allergy labels. This influenced the prevalence reported; detailed information in this regard is given in Table I. There were also differences based on country of study origin, cohort demographics, and the patient's medical condition across the studies. The overall prevalence of reported antibiotic allergy across all studies varied between 3% to 35% in adults, and around 5% of in children (Table I). Two studies reported that patients with an AAL were significantly older (70 y vs 63 y) and were more likely to be female (65% vs 35%). In addition, Lucas et al (2019)[4] also reported that, within pediatrics, antibiotic allergy increased with age. Three European studies, 1 from a Dutch University Hospital,[46] 1 from a Norwegian Hospital,[39] and 1 from a Spanish Hospital,[36] all relating to penicillin allergy, reported the lowest prevalence of AALs at 5.6% and 4.6% and 3%, respectively. Patients with cancer had the highest rates of antibiotic allergy reported, ranging from 23% to 35%.[42,43] Studies with a low reported prevalence (<5%) were heterogeneous, thus an association of a low prevalence with a specific cohort or patient characteristics could not be determined (Table I).

Impact of reported antibiotic allergy on antimicrobial prescribing

Alternative prescribing because of an AAL was the most reported impact (Table II), with between 30% and 60% of patients with an AAL receiving care with poorer concordance with common prescribing patterns than those without. Chakravorty et al (2022)[23] and Trubiano et al (2015)[43] separately reported that approximately 50% of patients with an antibiotic AAL had poorer concordance with prescribing patterns than those without, with a higher number of restricted antibiotics prescribed and an increase of fluoroquinolone and carbapenem use. Catalano et al (2022)[22] discussed a similar rate of alternative prescribing for patients with a beta-lactam AAL, with Jones et al (2017)[15] and Mason et al (2019)[34] also reporting a higher use of broader spectrum antibiotics within the beta-lactam allergy group. Powell et al (2021)[49] concurred and found that the penicillin AAL group were 4.7 times more likely to receive restricted antibiotics, and Trubiano et al (2015)[42] confirmed a higher use of beta-lactam antibiotics in the nonallergy group. Within pediatrics, Lucas et al (2019)[4] found that patients with an antibiotic allergy also received significantly more macrolide, quinolone, and lincosamide antibiotics and metronidazole. Furthermore, Gulholm et al (2021)[25] and MacFadden et al (2016)[6] found that patients with antibiotic AALs were more likely to suffer a significant adverse event as a result of inappropriate prescribing.

Impact of reported antibiotic allergy on clinical outcomes

A potential adverse clinical outcome for a patient with an AAL is the impact on length of hospital stay. Catalano et al (2022)[22] and Perez-Encinas et al (2022)[36] identified that the length of

hospital stay was longer for the penicillin AAL patients (median 4.7 d vs median 3.9 d), and Huang et al (2018)[28] concurred with these findings for the beta-lactam AAL group (11.3 vs 7.6 days). A pediatric study also concluded there was a significant increase in length of stay for those with an antibiotic AAL.[4] Trubiano et al (2015)[42,43] reported that the duration of antimicrobial therapy for patients with a reported antibiotic AAL was longer than for patients with no antibiotic allergy label (NAAL) and that patients with an AAL had an increased duration of therapy and readmission rates. MacFadden et al (2016)[6] found that patients with an AAL had an increased likelihood of adverse reactions and readmission rates. Van Dijk et al (2016)[46] and Huang et al (2018)[28] identify an increase of readmission rates for the beta-lactam AAL group. Knezevic et al (2016)[7] agreed that patients with an antibiotic AAL were significantly more likely to be readmitted within 4 weeks, 29% AAL patients compared with 18% NAAL patients; and patients with an AAL also had significantly more readmissions within 6 months, 30% of AAL compared with 19% NAAL.

Conway et al (2017)[2] examined the impact on the timing of an AAL to commencement of therapy and clinical outcomes and stated that having an AAL did lead to a delay in the commencement of antimicrobial therapy, but despite this delay, there were no significant differences in length of therapy, length of hospital admission, and readmission rates. However, they concede that the small sample size and older population may have limited their findings in comparison with other populations.

Antimicrobial use was also influenced by an AAL, with a higher use of non−beta-lactam alternatives, known to be linked to methicillin-resistant *Staphylococcus aureus* (MRSA) or *C. difficile* infections.[2,7] Chakravorty et al (2022)[23] and Huang et al (2018)[28] both found the incidence of developing *C. difficile* or MRSA was higher in patients with an antibiotic and beta-lactam AAL respectively. All the articles agreed that there was an adverse impact on clinical outcomes of patients with an AAL (Table II).

Delabeling strategies as an intervention, including risk stratification, to improve clinical outcomes

Antibiotic allergy delabeling was discussed as a strategy to improve patient care and clinical outcomes, and this was identified as an intervention for AAL assessment. Skin testing together with an oral challenge is the gold standard for confirming and/or delabeling AALs, however, throughout this review, different strategies were identified with novel strategies emerging over time (Figure 2).

Skin testing plus oral provocation challenge. Skin testing (skin prick testing and intradermal testing) together with an oral challenge is the historical approach for confirming and/or delabeling AALs.[50] Trubiano et al (2017)[45] introduced such testing within the inpatient hospital setting and measured the impact of this on clinical outcomes, while Taremi et al (2019)[41] tested a cohort of oncology patients who were immunocompromised. Both studies report that up to 95% of patients had an AAL revised with over 50% of patients having the label removed completely and/or having their therapy changed to a preferred beta-lactam therapy. Follow-up showed that use of the preferred antibiotic prescribing guidelines had significantly increased use of beta-lactam therapies.[41,45] Heil et al (2016)[27] concurred with patients (n = 90) who were deemed eligible undergoing skin testing and a single-dose amoxicillin challenge, 96% were delabeled and 84% had their antibiotic changed to a preferred beta-lactam.

Modi et al (2019)[35] retrospectively identified patients (n = 208) with a reported penicillin allergy and measured antibiotic use and incidence of *C. difficile* pre and post implementation of skin testing and oral challenges. They reported an increase in the use of beta-lactam antibiotics, decrease in the use of alternative antibiotics and decrease in the incidence of *C. difficile*.

Direct oral provocation challenge. MacFadden et al (2016)[6] suggest that patients with a mild history of rashes could be tested with a single oral dose of the culprit antibiotic with no skin testing. Tannert et al (2017),[50] who examined skin testing as a predictor of antibiotic allergy, found that skin testing alone was not reliable.

Studies are emerging that use risk stratification tools to distinguish between patients with a low-risk or a high-risk of reaction to antibiotic challenges, mainly to determine whether some patients can be safely delabeled by a direct oral challenge without skin testing or without any testing at all (direct delabeling). du Plessis et al (2019)[3] and Ham et al (2021)[26] examined AAL patients (n = 34 and n = 50, respectively) with a pharmacist-led allergy assessment interview, the latter using an institutional algorithm to categorize the patients as low risk, allowing them to be delabeled during the interview or to proceed directly onto an oral challenge. Over 90% of these patients were subsequently delabeled as a result. A similar process was undertaken by Livirya et al (2022),[32] in which 224 patients were screened and 50% were successfully delabeled.

Li et al (2021)[31] identified 149 patients and categorized them into low risk and non−low risk, with no history of anaphylaxis. All proceeded to a 1-step oral provocation with extended course, 94% to 100% of each group were delabeled.

Chua et al (2021)[24] also used a risk stratification tool to categorize patients (n = 1225) into low-risk and high-risk antibiotic allergy groups; 29%, all deemed low risk, were successfully delabeled, based on clinical history or by tolerating an oral challenge. Follow-up again showed an improvement in adherence to prescribing guidelines.

Direct and immediate delabeling. Inpatient delabeling may also provide immediate benefit because the antibiotic treatment can be changed to the preferred antibiotic regimen.[39] Sigona et al (2016)[38] conducted a study of 32 patients with a reported penicillin allergy. Patients were interviewed and a risk assessment was then undertaken; if appropriate, a recommendation to change to a preferred beta-lactam therapy was made, 21 patients changed therapy, which all of them tolerated. Steenvoorden et al (2021)[39] used an interview algorithm to screen patients admitted with a reported penicillin allergy. Eighty-six patients met the criteria for testing, 98% had no immediate reaction and had their label removed. Of those patients receiving antibiotic therapy, 42% had their therapy changed to a penicillin immediately after testing.

DISCUSSION

The total number of participants across all the studies was 1,089,675. Within these populations, the review showed that the prevalence of antibiotic allergy reporting remains high at between

TABLE II. Impact on clinical outcomes as assessed and reported by each listed study

Author and y	Alternative antimicrobial prescribing	Increase in length of stay	Increase in readmission	Longer duration of therapy	Increase in microbial resistance
Catalano et al (2022)[22]	✓	✓	-	-	-
Chakravorty et al (2022)[23]	✓	-	-	-	✓
Conway et al (2017)[2]	✓	-	-	-	-
Gulholm et al (2021)[25]	✓	-	-	-	-
Huang et al (2018)[28]	-	✓	✓	-	✓
Jones et al (2021)[29]	✓	-	-	-	-
Knezevic et al (2016)[7]	✓	-	✓	-	-
Lucas et al (2019)[4]	✓	✓	-	-	-
MacFadden et al (2016)[6]	✓	-	-	-	-
Mason et al (2019)[34]	✓	-	-	-	-
Perez-Encinas et al (2022)[36]	-	✓	-	-	-
Powell et al (2022)[19]	✓	-	-	-	-
Seidelman et al (2022)[37]		-	-	✓	-
Trubiano et al (2015)[42]	✓	-	-	✓	-
Trubiano et al (2015)[43]	-	-	✓	✓	-
Trubiano et al (2016)[44]	-	-	-	-	-
Van Dijk et al (2016)[46]	✓	-	✓	-	-

5% to 35% of the adult population; however, this can vary based on type of antibiotic AAL studied, country, and demographics.[42,43] The lowest rates were reported in Europe; cancer patients reported the highest rates, most likely due to higher antibiotic exposure within this population.

In children, the prevalence increases with age, the lowest being in children younger than 5 years.[4,7] The pediatric studies within this review show lower prevalence of AALs and less impact on clinical outcomes than seen within the adult population. Overall, there are fewer studies in pediatric populations and the prevalence of AALs in children is lower; thus, further large cohort studies are required to detect an impact of AALs on clinical outcomes in children.

Our review also highlights the impact a reported antibiotic allergy has on the avoidance of first-line antibiotics and increased use of alternative antimicrobials, a behavior that is associated with antibiotic resistance.[7,8] The AALs can lead to alternative antimicrobial prescribing and contribute to the 30% to 60% of inappropriate antibiotic usage in American acute care hospitals.[51] This review reported up to 50% of patients with an antibiotic allergy did not receive the preferred therapy, with a higher use of quinolone, glycopeptide macrolides, and carbapenem antibiotics.[4,29,22] A small group of the studies demonstrated that this alternative use of antimicrobials is linked to severe antibiotic-resistant infections such as MRSA and *C. difficile*.[8] In addition, patients are more likely to receive treatment failure as a result or suffer a significant adverse event as a result of inappropriate prescribing.[7,23,52] This potentially leads to poorer clinical outcomes such as longer duration of antimicrobial therapy or a delay in appropriate treatment, leading to longer hospital stays, with patients more likely to be readmitted in 4 weeks and have 2 or more readmissions within 6 months.[2,6,7,22]

These findings highlight the need for strategies to delabel or confirm AALs, with antibiotic delabeling to improve patient clinical outcomes emerging as a theme. This is predominantly evident in the later studies within this review. Details how delabeling strategies have been developed over the last 3 years, from the original standard of skin testing plus oral challenge to new initiatives for direct delabeling, including risk stratification, are illustrated in Figure 2. Skin testing and an oral challenge was discussed by several studies as an initiative to delabel patients as inpatients to improve clinical outcomes under AMS programs; however, a lack of specialists available within the hospital setting could be a foreseeable barrier to this.[35,44,45] Those that did introduce this as an initiative found that over 90% of patients were delabeled of their penicillin allergy and over 50% had their antibiotic changed to the preferred therapy.[24,27,31,35,41,45] A decrease in the use of alternative antibiotics as a result and an increase in the beta-lactam antibiotics, together with a decrease in the incidence of *C. difficile,* was also reported.[24,35,39]

Furthermore, strategies for direct delabeling that included taking an initial accurate and detailed history, whereby those with a clear history of a mild reaction could be delabeled without the need for challenge or direct oral challenge, with a single-dose challenge without the need for skin testing, were discussed and implemented by several studies and found that over 80% to 90% of patients were successfully delabeled using this method.[6,24,26,31,39,53] Based on the current knowledge of the complications that such prescribing can create and its potential impact on hospital length of stay and readmission rates, these studies highlight the growing need for such strategies to delabel and/or confirm AALs to improve clinical outcomes for these patients.[7]

Some of the studies felt further research implementing allergy assessment clinics,[2,44] together with inpatient assessment programs and delabeling strategies, could improve health care utilization and improve narrow-spectrum antibiotic use.[6,33,49] However, it could be argued that the need for inpatient delabeling should be risk-stratified in terms of inpatient populations that have a clinical need for delabeling at the time of admission. This may also be dependent of the accessibility of an allergy department with the relevant expertise[54] versus those that could be assessed within outpatient settings and potentially integrated in community care.

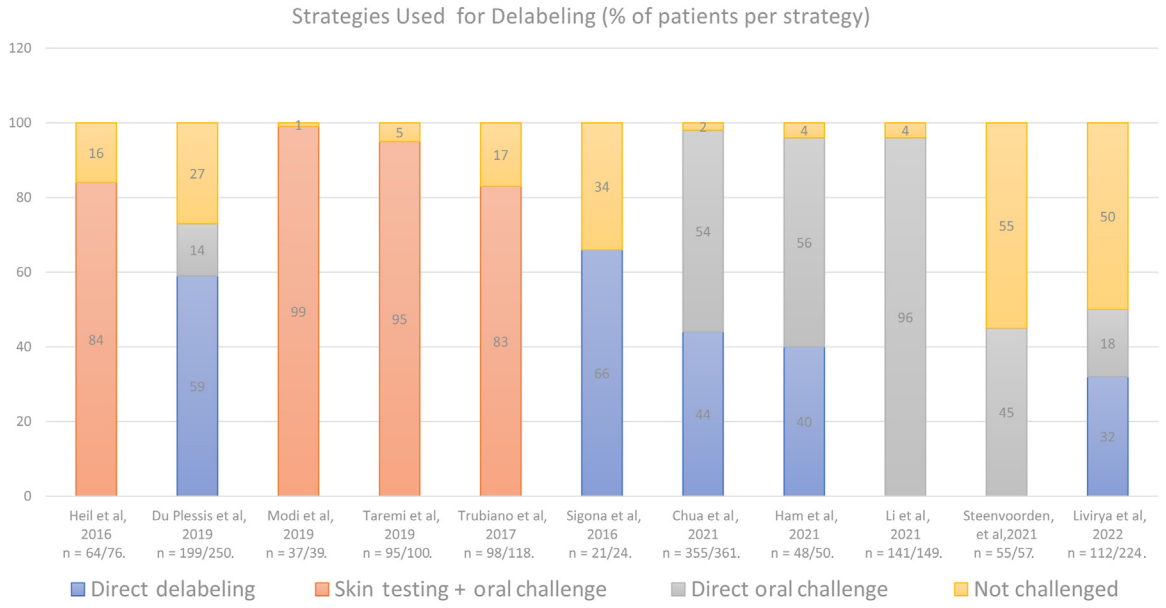

FIGURE 2. Delabeling strategies developed over time (n = delabeled/total challenged).

Strengths and limitations

This review included the most up-to-date studies reporting the impact of antibiotic allergy on clinical management, and emerging strategies for delabeling. The PRISMA guidelines[21] were used to conduct the search, and methodological quality was assessed for risk of bias using the JBI Critical Appraisal Tool for systematic reviews. A limitation of our review was that prevalence was not specifically within the inclusion criteria; therefore, some prevalence studies have been missed. In addition, the review generated studies from developing countries, the United States, Europe, and Australasia. There is limited literature available from certain regions, including Asian centers, and therefore, this review may not be a true global representation.

Many studies reported on the limitations that may have impacted on their results. A single center or single population may limit application to other centers or populations,[41] and a single center health care system may mean that generalization outside of the region is uncertain and may not represent other hospital cohorts.[29,49] Small sample size was also addressed in 5 studies, which may limit findings to other populations.[23,30,38,42,55]

Retrospective design studies rely on accurate and proper documentation, and this can limit the information drawn, potentially creating bias; therefore, some patients may have been missed and the prevalence of reported beta-lactam allergy may be inaccurate.[5,28,35] In addition, it could be subject to selection bias and misclassification bias and maybe not all patients were correctly identified.[37] Furthermore, AMS is a set of interventions that aim to assist clinicians in terms of optimal selection of antimicrobials; AMS targets, interventions, and initiatives may have influenced the antibiotic selection and change in antimicrobial use.[5,41,44]

The studies within this review were mainly biased toward inpatients, predominantly recruited within the context of infectious disease services and AMS and this may have impacted the results of this review. Three studies that did address patients within the outpatient setting reported similar outcomes to those with inpatient population, with improved prescribing, fewer outpatient visits, or hospital presentations and improved delabeling practices. However, limited data are available within outpatient settings, and these few studies may not be a true representation of this population; therefore, this highlights the need for larger studies within this area.[5,44]

CONCLUSIONS

This review identified that AALs do have a significant impact on inpatient admissions in terms of length of stay, antimicrobial prescribing, antimicrobial resistance, and readmissions. Whereas the U.S. Drug Allergy Practice Parameters provide an evidence-based approach for the diagnosis and management of adverse drug reactions, this review examined delabeling practices and their clinical impact internationally. There is heterogeneity in current practice of assessing antibiotic allergy, and a need to review and streamline diagnostic procedures to be safe, accurate, and cost effective globally.[54] Furthermore, there is limited literature available from certain regions, including Asian centers, and even less that examined the prevalence within pediatrics. Several studies show the impact of AAL delabeling on patients' outcomes, but further studies are needed to prospectively assess the effectiveness of delabeling strategies in various divergent health care settings, including pediatrics. The emerging issue of relabeling discussed within current literature will also need to be closely monitored.[56] In addition, this review identified a lack of health economics analysis to establish the cost effectiveness of delabeling versus the impact of AALs. Ideally, prospective randomized studies, in both the hospital and the primary care setting, are necessary to facilitate this.

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ONLINE REPOSITORY

FIGURE E1. Search strategies.

PubMed

Search ((((((Penicillin allergy) OR beta lactam allergy) OR antibiotic allergy) OR cephalosporin allergy)) AND ((antimicrobial stewardship programme) OR infectious diseases)) AND effect on health Filters: published in the last 10 years

Search ((((((Penicillin allergy) OR beta lactam allergy) OR antibiotic allergy) OR cephalosporin allergy)) AND ((antimicrobial stewardship programme) OR infectious diseases)) AND effect on health Search ((((((Penicillin allergy) OR beta lactam allergy) OR antibiotic allergy) OR cephalosporin allergy)) AND ((antimicrobial stewardship programme) OR infectious diseases)) AND ((inappropriate prescribing) OR alternative prescribing)

Search ((((((hospital length of stay) OR readmissions) OR antimicrobial resistance) OR reinfection)) AND ((inappropriate prescribing) OR alternative prescribing)) AND ((((Penicillin allergy) OR beta lactam allergy) OR antibiotic allergy) OR cephalosporin allergy)

Search (((((((hospital length of stay) OR readmissions) OR antimicrobial resistance) OR reinfection)) AND ((inappropriate prescribing) OR alternative prescribing)) AND ((antimicrobial stewardship programme) OR infectious diseases)) AND ((((Penicillin allergy) OR beta lactam allergy) OR antibiotic allergy) OR cephalosporin allergy)

Search ((((((Penicillin allergy) OR beta lactam allergy) OR antibiotic allergy) OR cephalosporin allergy)) AND ((antimicrobial stewardship programme) OR infectious diseases)) AND ((((hospital length of stay) OR readmissions) OR antimicrobial resistance) OR reinfection) Search (((((((Penicillin allergy) OR beta lactam allergy) OR antibiotic allergy) OR cephalosporin allergy)) AND ((antimicrobial stewardship programme) OR infectious diseases)) AND ((inappropriate prescribing) OR alternative prescribing)) OR ((((hospital length of stay) OR readmissions) OR antimicrobial resistance) OR reinfection)

Search (((hospital length of stay) OR readmissions) OR antimicrobial resistance) OR reinfection

Search (inappropriate prescribing) OR alternative prescribing

Search (antimicrobial stewardship programme) OR infectious diseases

Search (((Penicillin allergy) OR beta lactam allergy) OR antibiotic allergy) OR cephalosporin allergy

Embase

('penicillin allergy'/exp OR 'penicillin allergy' OR (('penicillin'/exp OR penicillin) AND ('allergy'/exp OR allergy)) OR 'beta lactam allergy' OR (beta AND ('lactam'/exp OR lactam) AND ('allergy'/exp OR allergy)) OR 'antibiotic allergy' OR (('antibiotic'/exp OR antibiotic) AND ('allergy'/exp OR allergy)) OR 'cephalosporin allergy':af) AND ('antimicrobial stewardship programme' OR (('antimicrobial'/exp OR antimicrobial) AND stewardship AND programme) OR 'infectious diseases'/exp OR 'infectious diseases' OR (infectious AND ('diseases'/exp OR diseases)))AND ('length of hospital stay' OR (('length'/exp OR length) AND of AND ('hospital'/exp OR hospital) AND stay) OR 'hospital readmission'/exp OR 'hospital readmission' OR 'reinfection'/exp OR reinfection OR 'antimicrobial resistance':af)

('penicillin allergy'/exp OR 'penicillin allergy' OR (('penicillin'/exp OR penicillin) AND ('allergy'/exp OR allergy))OR 'beta lactam allergy' OR (beta AND ('lactam'/exp OR lactam) AND ('allergy'/exp OR allergy)) OR 'antibiotic allergy' OR (('antibiotic'/exp OR antibiotic) AND ('allergy'/exp OR allergy)) OR 'cephalosporin allergy':af) AND ('antimicrobial stewardship programme' OR ('antimicrobial'/exp OR antimicrobial) AND stewardship AND programme) OR

'infectious diseases'/exp OR 'infectious diseases' OR (infectious AND ('diseases'/exp OR diseases))) AND ('alternative prescribing' OR (alternative AND prescribing) OR 'inappropriate prescribing'/exp OR 'inappropriate prescribing' OR (inappropriate AND prescribing))

'length of hospital stay' OR (('length'/exp OR length) AND of AND ('hospital'/exp OR hospital) AND stay) OR 'hospital readmission'/exp OR 'hospital readmission' OR 'reinfection'/exp OR reinfection OR 'antimicrobial resistance':af

'alternative prescribing' OR (alternative AND prescribing) OR 'inappropriate prescribing'/exp OR 'inappropriate prescribing' OR (inappropriate AND prescribing)

'antimicrobial stewardship programme' OR (('antimicrobial'/exp OR antimicrobial) AND stewardship AND programme) OR 'infectious diseases'/exp OR 'infectious diseases' OR (infectious AND ('diseases'/exp OR diseases))

'penicillin allergy'/exp OR 'penicillin allergy' OR (('penicillin'/exp OR penicillin) AND ('allergy'/exp OR allergy)) OR 'beta lactam allergy' OR (beta AND ('lactam'/exp OR lactam) AND ('allergy'/exp OR allergy)) OR 'antibiotic allergy' OR (('antibiotic'/exp OR antibiotic) AND ('allergy'/exp OR allergy)) OR 'cephalosporin allergy':af

CINAHL

antimicrobial stewardship.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
infectious disease*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
penicillin allerg*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
antibiotic allerg*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
beta lactam allerg*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
cephalosporin allerg*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
clinical outcome*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
antimicrobial resistance.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
mortality.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy

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(alternative prescribing):ti,ab,kw OR (inapproriate prescribing):ti,ab,kw
(antimicrobial stewardship programme):ti,ab,kw OR (infectious diseases):ti,ab,kw
(length of hospital stay):ti,ab,kw OR (readmissions):ti,ab,kw OR (reinfection):ti,ab,kw OR (antimicrobial resistance):ti,ab,kw
(effect on health):ti,ab,kw
(penicillin allergy):ti,ab,kw OR (beta lactam allergy):ti,ab,kw OR (antibiotic allergy):ti,ab,kw OR (cephalosporin allergy):ti,ab,kw

(continued)

FIGURE E1. *(Continued)*

Medline
antimicrobial stewardship.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
infectious disease*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
penicillin allerg*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
antibiotic allerg*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
beta lactam allerg*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
cephalosporin allerg*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
clinical outcome*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
antimicrobial resistance.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
mortality.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy

TABLE E1. Logic grid with keywords and index terms or subject headings

Population	Intervention	Comparison	Outcome
Patients with reported penicillin allergy	Antimicrobial Stewardship Program	Patient with no reported penicillin allergy	Impact on clinical outcomes
Cephalosporin allergy	Infectious diseases	Standard care	Length of stay
Beta-lactam allergy	*MH infectious diseases medicine*		Antimicrobial resistance
Antibiotic allergy			Readmission rates
MH beta-lactams			Intensive care admissions
MH penicillins			Mortality
			MH intensive care units
			MH intensive care
			MH drug resistance, microbial
			MH mortality

MH, Medical Subject Heading (MeSH); *PICO,* Population, Intervention, Comparison, and Outcome framework.
Eriksen MB, Frandsen TF. The impact of patient, intervention, comparison, outcome (PICO) as a search strategy tool on literature search quality: a systematic review. J Med Libr Assoc 2018;106:420-31.

TABLE E2. Joanna Briggs Institute Critical Appraisal Checklist for Systematic Reviews

Critical appraisal table for cohort studies without an intervention (n = 16)

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Total yes
Conway et al[2]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	10
Catalano et al[22]	Y	Y	Y	N	N	Y	Y	Y	NA	NA	Y	7
Chakravorty et al[23]	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	Y	9
Huang et al[28]	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	10
Jones et al[15]	Y	Y	Y	Y	Y	U	Y	Y	Y	NA	NA	8
Knezevic et al[7]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11
Lucas et al[4]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11
MacFadden et al[6]	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	9
Mason et al[34]	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	10
Perez et al[36]	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	10
Powell et al[19]	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	NA	8
Seidelman et al[37]	Y	Y	Y	Y	Y	U	Y	NA	NA	NA	Y	7
Trubiano et al[42]	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	9
Trubiano et al[43]	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	10
Trubiano et al[44]	Y	Y	Y	N	Y	Y	Y	Y	Y	NA	Y	9
Van Dijk et al[46]	Y	Y	Y	U	U	Y	Y	Y	Y	NA	Y	8

Q1. Were the 2 groups similar and recruited from the same population? Q2. Were the exposures measured similarly to assign people to both exposed and unexposed groups? Q3. Was exposure measured in a valid and reliable way? Q4. Were confounding factors identified? Q5. Were strategies to deal with confounding factors stated? Q6. Were the groups/participants free of the outcome at the start of study (or at the moment of exposure)? Q7. Were the outcomes measured in a valid and reliable way? Q8. Was the follow-up time reported and sufficient to be long enough for outcomes to occur? Q9. Was the follow-up complete, and if not, were the reasons for loss to follow-up described and explored? Q10. Were strategies to address incomplete follow-up utilized? Q11. Was appropriate statistical analysis used?

Critical appraisal table for cohort studies with an intervention (n = 10)

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Total yes
du Plessis et al[3]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	9
Heil et al[27]	Y	Y	Y	N	N	Y	Y	Y	N	N	Y	7
Li et al[31]	Y	Y	Y	N	N	Y	Y	Y	N	N	Y	7
Phan et al[5]	Y	Y	Y	Y	N	N	Y	Y	N	N	Y	7
Macy & Shu[13]	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	10
Modi et al[35]	Y	Y	Y	Y	U	Y	Y	Y	Y	NA	Y	9
Sigona et al[38]	U	U	Y	U	U	Y	Y	U	Y	NA	Y	5
Swearingham et al[40]	Y	Y	Y	N	N	N	Y	Y	N	N	Y	6
Taremi et al[41]	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y	8
Trubiano et al[45]	Y	Y	Y	N	NA	Y	Y	Y	Y	NA	Y	8

Q1. Were the two groups similar and recruited from the same population? Q2. Were the exposures measured similarly to assign people to both exposed and unexposed groups? Q3. Was exposure measured in a valid and reliable way? Q4. Were confounding factors identified? Q5. Were strategies to deal with confounding factors stated? Q6. Were the groups/participants free of the outcome at the start of study (or at the moment of exposure)? Q7. Were the outcomes measured in a valid and reliable way? Q8. Was the follow-up time reported and sufficient to be long enough for outcomes to occur? Q9. Was the follow-up complete, and if not, were the reasons for loss to follow-up described and explored? Q10. Were strategies to address incomplete follow-up utilized? Q11. Was appropriate statistical analysis used?

Critical appraisal table for case series studies without an intervention (n = 1)

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Total # 'Yes'
Gulholm et al[25]	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	9

Critical appraisal table for case series studies with an intervention (n = 4)

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Total yes
Ham et al[26]	Y	Y	Y	N	N	Y	Y	Y	N	U	6
Li et al[31]	Y	Y	Y	Y	U	Y	Y	Y	N	U	7
Livirya et al[32]	Y	Y	Y	U	Y	Y	Y	Y	Y	U	8
Steenvoorden et al[39]	Y	Y	Y	U	U	Y	Y	Y	Y	U	7

Q1. Were there clear criteria for inclusion in the case series? Q2. Was the condition measured in a standard, reliable way for all participants included in the case series? Q3. Were valid methods used to for identification of the condition for all participants included in the case series? Q4. Did the case series have consecutive inclusion of participants? Q5. Did the case series have complete inclusion of participants? Q6. Was there clear reporting of the demographics of the participants in the study? Q7. Was there clear reporting of clinical information of the participants? Q8. Were the outcomes or follow-up results of cases clearly reported? Q9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information? Q10. Was statistical analysis appropriate?

Critical appraisal table for quasi-experimental studies with an intervention (n = 1)

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Total yes
Chua et al[24]	Y	Y	N	Y	Y	Y	Y	Y	Y	8

Q1. Is it clear in the study what is the "cause" and what is the "effect" (ie, is there is no confusion about which variable comes first? Q2. Were the participants included in any comparisons similar? Q3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest? Q4. Was there a control group? Q5. Were there multiple measurements of outcome both pre and post the intervention/exposure? Q6. Was follow-up complete, and if not, were differences between the 2 groups in terms of their follow-up adequately described and analyzed? Q7. Were the outcomes of the participants included in any comparisons measured in the same way? Q8. Were outcomes measured in a reliable way? Q9. Was appropriate statistical analysis used?

NA, Not applicable; *U,* unclear.