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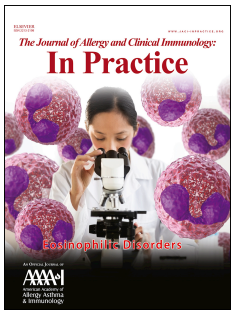

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Title Page

The burden of self-reported antibiotic allergies in healthcare and how to address it: a systematic review of the evidence

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ABSTRACT

Background

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

Objective

A systematic review was conducted to summarise 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 5-35%. Patients with a reported antibiotic allergy, had poorer concordance with prescribing guidelines in 30-60% 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.

Conclusion

There is substantial evidence within the literature that antibiotic allergy labels significantly impact on patient clinical outcomes and a consensus that systematic assessment of reported antibiotic allergies, commonly referred to as “delabeling”, improves the clinical management of patients.

Highlights

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 10-15% of the adult population internationally have 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 standardised, safe, accurate and cost-effective manner, to optimise patient care.

Key Words

Antibiotic allergy, delabeling, antimicrobial stewardship, drug allergy

Abbreviations

AAL -	Antibiotic Allergy Labels
AMS -	Antimicrobial Stewardship
C. diff. -	Clostridium difficile
ID -	Infectious Diseases
MRSA -	Methicillin-Resistant Staphylococcus Aureus
NAAL -	No Antibiotic Allergy Labels
PICO -	Population, Intervention, Comparison and Outcome
PRISMA -	Preferred Reporting Items for Systematic Reviews and Meta-analyses
VRE -	Vancomycin-Resistant Enterococcus

1. INTRODUCTION

Antimicrobial resistance is increasing whilst 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 10-15% of the adult population internationally have reported antibiotic allergy labels (AAL) 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 healthcare 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 (VRE), Methicillin-Resistant Staphylococcus Aureus (MRSA) and Clostridium difficile *(C. diff.)*.[7-9]

Reported antibiotic allergy in children is also increasing,[10] the majority having an AAL against a beta-lactam antibiotic.[10,11] Within paediatrics, 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 paediatric population, AAL create a barrier to AMS with clinical and economic implications.[15] Antimicrobial Stewardship is an

112 international concept of reducing inappropriate antibiotic use to improve the safe and appropriate use
113 of antibiotics within Australian hospitals.
114
115 Whilst other systematic reviews have examined aspects of penicillin allergy management,[16-19] this
116 systematic review examines both the impact of antibiotic allergy, including penicillin and beta-lactam
117 allergy, on patient clinical outcomes, together with current and novel strategies to effectively delabel
118 AAL, from an adult and paediatric perspective.
119
120 **2. METHODS**
121
122 **2.1 Inclusion Criteria**
123
124 This literature review was conducted using the population, intervention, comparison and outcome
125 (PICO) framework (Table E1).[20] The population of interest identified patients admitted to hospital with
126 a reported antibiotic allergy including beta-lactam, penicillins and cephalosporins. The intervention
127 included patients who were admitted under or reviewed by Infectious Diseases or Antimicrobial
128 Stewardship services, with the comparison being patients admitted to hospital under the same
129 speciality, with no reported beta-lactam allergy, receiving standard care. The outcome examined the
130 impact of antibiotic allergy on clinical outcomes, such as length of hospital stay, inappropriate
131 prescribing, readmission, and mortality.
132

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 speciality or age of patients studied.

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).

2.2 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 United States Library of Medicine (PubMed) and the Cochrane Library. The full search strategy, including search terms, is provided in Figure E1.

2.3 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 two of three reviewers (AA, LC,

MF), who independently screened titles and abstracts, excluding studies that did not meet the inclusion criteria. Two reviewers in pairs (AA, LC, MF) also did full text screening of articles, with any study that did not meet the inclusion criteria being excluded. Identified disagreements were resolved between the reviewers through discussion or with the third reviewer.

2.4 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 one of four ratings (yes, no, unclear or not applicable). Each article was assessed by two of three reviewers (AA, LC, MF) and disagreements were resolved between the reviewers through discussion or with the third reviewer (Table E2).

2.5 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 1).

Due to heterogeneity of outcome measures, a meta-analysis of quantitative data could not be completed. A narrative synthesis was completed to report the findings.[22]

3. 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. Total articles included in this review were 32 (Figure 1).

These articles were then assessed by two independent viewers (AA, LC, MF), for methodological quality, using the JBI Critical Appraisal Tool as represented in Table E2.[23] 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 study. (Table E2).

The studies included in this review were published from 2015 to 2022, originating from the United States of America (USA),[2,5,24-34] Canada,[6] Australia,[4,35-44] New Zealand,[3,45] United Kingdom,[46] Spain,[47] Norway,[48] and the Netherlands (Table 1).[49] The studies were cohort studies, case series and quasi-experimental studies and comprised of surveys,[40] retrospective reviews,[2,4,5,26,27,30-32,35,36,38,40-43,46,47,49] case series,[24,38,39,45,48] quasi-experimental,[37] and prospective cohort studies.[3,6,25,28,29,33,34,39,44] 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 four 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 influenced by the reported AAL 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.

3.1 Prevalence of Reported Antibiotic Allergy

Seventeen studies examined patients with a penicillin allergy label, eight studies examined patients with a beta-lactam allergy label, the remaining seven studies reported on all antibiotic allergy labels. This influenced the prevalence reported; detailed information in this regard is given in Table 1. 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 1). Two studies reported that patients with an AAL were significantly older (70 years vs 63 years) and were more likely to be female (65% vs 35%). In addition, Lucas et al (2018) also reported that within paediatrics antibiotic allergy increased with age. [4,46,47] Three European studies, one from a Dutch University Hospital, one from a Norwegian Hospital and one from a Spanish Hospital, all relating to penicillin allergy, reported the lowest prevalence of AAL at 5.6% and 4.6% and 3% respectively. [47,48,49] Patients with cancer had the highest rates of antibiotic allergy reported, ranging from 23% to 35%.[40,41] Studies with a low reported prevalence (<5%) were heterogenous, thus an association of a low prevalence with a specific cohort or patient characteristics could not be determined (Table 1).

3.2 Impact of Reported Antibiotic Allergy on Antimicrobial Prescribing

Alternative prescribing because of an AAL, was the most reported impact (Table 2), with between 30% to 60% of patients with an AAL receiving care with poorer concordance with common prescribing patterns than those without. Chakravorty et al (2022) and Trubiano et al. (2015) 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.[29,36,41] Catalano et al. (2022) discussed a similar rate of alternative prescribing for patients with a beta-lactam AAL, with Jones et al. (2022) and Mason et al. (2019) also reporting a higher use of broader spectrum antibiotics within the beta-lactam allergy group. [15, 29,35] Powell et al. (2021) concurred and found that the penicillin AAL group were 4.7 times more likely to receive restricted antibiotics and Trubiano et al. (2015) confirmed a higher use of beta-lactam antibiotics in the non-allergy group.[35,40,46] Within paediatrics, Lucas et al. (2018) found that patients with an antibiotic allergy also received significantly more macrolide, quinolone, lincosamide antibiotics and metronidazole.[4] Furthermore, Gulholm et al. (2021) and MacFadden et al. (2016) found that patients with antibiotic AAL were more likely to suffer a significant adverse event as a result of inappropriate prescribing.[6,38]

3.3 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. (2021) and Perez-Encinas et al. (2021) identified that the length of hospital stay was longer for the penicillin AAL patients (median 4.7 days vs median 3.9 days) and Huang et al. (2018)

concurred with these findings for the beta-lactam AAL group (11.3 vs 7.6 days).[2,26,35] A paediatric study also concluded there was a significant increase in length of stay for those with an antibiotic AAL.[4] Trubiano et al. (2015) reported the duration of antimicrobial therapy for patients with a reported antibiotic AAL was longer than patients with no antibiotic allergy label and that patients with an AAL had an increased duration of therapy and readmission rates.[40,41] MacFadden et al. (2016) found patients with an AAL had an increased likelihood of adverse reactions and readmission rates. Van Dijk (2016) and Huang et al. (2018) identify an increase of readmission rates for the beta-lactam AAL group.[6,26,49] Knezevic et al. (2016) agreed that patients with an antibiotic AAL were significantly more likely to be re-admitted within four weeks, 29% AAL patients compared to 18% no label, and patients with an AAL also had significantly more readmissions within six months, 30% of AAL compared to 19% no label.[6,7]

Conway et al. (2017) 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 to other populations.[50]

Antimicrobial use was also influenced by an AAL, with a higher use of non-beta-lactam alternatives, known to be linked to MRSA or *C.diff.* infections.[2,7] Chakravorty et al. (2022) and Huang et al. (2018) both found the incidence of developing *C.diff* or MRSA was higher in patients with an antibiotic and beta-lactam AAL respectively.[26,36] All the articles agreed that there was an adverse impact on clinical outcomes of patients with an AAL (Table 2).

3.4 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 AAL, however, throughout this review, different strategies were identified with novel strategies emerging over time (Figure 2.).

3.4.1 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 AAL.[51] Trubiano et al. (2017) introduced such testing within the inpatient hospital setting and measured the impact of this on clinical outcomes, while Taremi et al. (2019) 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 had the label removed completely and/or had 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.[34,43] Heil et al. (2016) 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.[25]

Modi et al. (2019) retrospectively identified patients (n=208) with a reported penicillin allergy and measured antibiotic use and incidence of *C.diff.* pre and post implementation of skin testing and oral

294 challenges. They reported an increase in the use of beta-lactam antibiotics, decrease in the use of
295 alternative antibiotics and decrease in the incidence of *C.diff.*[30]
296
297 3.4.2 Direct oral provocation challenge
298 MacFadden et al. (2016) suggest that patients with a mild history of rashes could be tested with a single
299 oral dose of the culprit antibiotic with no skin testing.[6] Tannert et al. (2017) who examined skin testing
300 as a predictor of antibiotic allergy found that skin testing alone was not reliable.[52]
301 Studies are emerging that use risk stratification tools to distinguish between patients with a low-risk or
302 high-risk of reaction to antibiotic challenges, mainly to determine whether if some patients can be
303 safely delabeled by a direct oral challenge without skin testing or without any testing at all (direct
304 delabeling). Du Plessis et al. (2019) and Ham et al. examined AAL patients (n=34 and n=50) with a
305 pharmacist led allergy assessment interview, the latter using an institutional algorithm to categorise
306 the patients, as low risk, allowing them to be delabeled during the interview or to proceed directly onto
307 an oral challenge. Over 90% of these patients were subsequently delabeled as a result. A similar process
308 was undertaken by Livirya et al. (2022), where 224 patients were screened and 50% were successfully
309 delabeled.[45]
310
311 Li et al. (2021) identified 149 patients and categorised them into low-risk and non-low risk, with no
312 history of anaphylaxis. All proceeded to a one step oral provocation with extended course, 94%-100%
313 of each group were delabeled.[39]
314
315 Chua et al. (2021) also used a risk stratification tool to categorise patients (n=1225) into low-risk and
316 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 .[37]

3.4.3 Direct and immediate delabeling

Inpatient delabeling may also provide immediate benefit as the antibiotic treatment can be changed to the preferred antibiotic regimen.[48] Sigona et al. (2020) conducted 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.[32] Steenvoorden et al. (2021) 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.[48]

4. 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 5% to 35% of the adult population, however, this can vary based on type of antibiotic AAL studied, on country and demographics.[40,41] The lowest rates were reported in Europe, and cancer patients reporting 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 under five.[4,7] The paediatric studies within this review show lower prevalence of AAL and less impact on clinical outcomes than seen within the adult population. Overall, there are fewer studies in paediatric populations and prevalence

of AAL in children is lower, thus further large cohort studies are required to detect an impact of AAL 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 behaviour that is associated with antibiotic resistance.[7,8] AAL can lead to alternative antimicrobial prescribing and contribute to the 30% to 60% of inappropriate antibiotic usage in American acute care hospitals.[53] 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. [4,27,35] 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.diff.*[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.[7,36,54] 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 four weeks and have two or more readmissions within six months.[2,6,7,35]

These findings highlight the need for strategies to delabel or confirm AAL, 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 three 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.[30,42,43] 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.[25,30,34,37,39,43] 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.diff.,* was also reported.[30,37,48]

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.[6,24,37,39,48,52] 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 AAL to improve clinical outcomes for these patients.[7]

Some of the studies felt further research implementing allergy assessment clinics, [2,42] together with inpatient assessment programmes and delabeling strategies, could improve healthcare utilisation and improve narrow spectrum antibiotic use.[6,28,46] 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,[55] versus those that could be assessed within outpatient settings and potentially integrated in community care.

4.2 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 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [21] was used to conduct the search and methodological quality was assessed for risk of bias using the Joanna Briggs Institute 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. Additionally, the review generated studies from developing countries, USA, Europe, and Australasia. There is limited literature available from certain regions, including Asian centres, 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 centre or single population may limit application to other centres or populations,[34] and a single centre healthcare system may mean that generalisation outside of the region is uncertain and may not represent other hospital cohorts.[27,46] Small sample size was also addressed in five studies, which may limit findings to other populations.[32,36,40,44,50]

Retrospective design studies are reliant 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. [5,26] [30] Additionally, it could be subject to selection bias and misclassification bias and may be not all patients were correctly identified.[31] Furthermore, AMS is a set of interventions that aim to assist clinicians in terms of optimal selection of

antimicrobials and AMS targets, interventions and initiatives may have influenced the antibiotic selection and change in antimicrobial use.[5,34,42]

The studies within this review were mainly biased towards inpatients, predominantly recruited within the context of infectious diseases services and antimicrobial stewardship 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, there is limited data 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.[5,42]

5. CONCLUSION

This review identified that AAL do have a significant impact on inpatient admissions in terms of length of stay, antimicrobial prescribing, antimicrobial resistance, and readmissions. Whilst the US 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.[55] Furthermore, there is limited literature available from certain regions, including Asian centres, and even less that examined the prevalence within paediatrics. 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 healthcare settings, including paediatrics. The emerging issue of relabelling 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 antibiotic allergy labels. Ideally, prospective randomised studies, both in the hospital and primary care setting, are necessary to facilitate this.

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629 Figure and Table Legends

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631 Figure 1. PRISMA 2020 flow diagram for updated systematic reviews which included searches of
632 databases and registers only

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634 Figure 2. Delabeling strategies developed over time.

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636 Table 1. Data Extraction Appraisal Table

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638 Table 2. Impact on Clinical Outcomes as assessed and reported by each listed study

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Table 1.

Author, Year And Country	Leading Team	Study Design	Sample size/Participants/Age	Prevalence/type of Reported AAL	Key Results	Intervention
Catalano *et al.* (2021) [35] Australia (Melbourne)		Retrospective Cohort Study	N = 938 children admitted to a tertiary children's hospital Age: 0-18 years	1% Beta-lactam	AAL increased the use inappropriately prescribed restricted antibiotics. Hospital length of stay was longer for AAL group.	None
Chakravorty *et al.* (2022) [36] Australia (Perth)		Retrospective Cohort Study	N = 630 referred for antimicrobial prospective audit and feedback rounds. Mean Age: 62 years	16% All Antibiotics	Patients with AAL were less likely to receive guideline recommended therapy. Higher incidence of developing *C.diff.* or MRSA in AAL group. Drug allergy documentation was generally poor.	None
Chua *et al.* (2021) [37] Australia (Melbourne)	Infectious Diseases and Immunology	Quasi-experimental Study	N = 1791 acute inpatients identified with a reported antibiotic allergy Median Age: 66 years	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] USA (New York)	Infectious Diseases	Retrospective Cohort Study	N = 403 veterans admitted through ED at a Veteran Affairs Healthcare Centre Mean Age: 75 years	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 specialising in infectious diseases and antimicrobial stewardship Age: 16-70 years	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) [38] Australia (New South Wales)	Infectious Diseases	Cohort Study	N = 844 a convenience sample presenting to ED in an adult teaching hospital. Age: 16-98 years	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) [24] USA (Oregan)		Case Series	N= 50 patients admitted to an academic medical centre. Age: 21-87 years	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 one 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.

Author Article, Year And Country	Leading Team	Study Design	Sample size/ Participants	Prevalence/type of Reported AAL	Key Results	Intervention
Heil *et al.* (2016) [25] USA (Maryland)	Infectious Diseases	Prospective Cohort Study	N = 90 admitted to an Academic Medical Centre 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 ID fellow led penicillin skin testing service.
Huang *et al.* (2018) [26] USA (Pennsylvania)	Immunology	Retrospective Cohort Study	N = 4671 patients with hematologic malignancy admitted to two tertiary care hospitals Mean Age: 60 years	35% Beta-lactam	Patients with a AAL had a significantly longer length of stay and significantly higher mortality rate at 30 days and 180 days; with a higher readmission rate at 30 days and increased *C.diff.* rate.	None
Jones *et al.* (2021) [27] USA (Utah)	Immunology	Retrospective Cohort Study	N = 38,906 paediatric patients 30 hospitalised between 2007 and 2017 Age: 1 month -17 years	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 hospitalisation	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 years	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) [44] Australia (New South Wales)	Immunology and Infectious Diseases	Prospective Cohort Study	N = 71 admitted to a tertiary hospital. Median Age: 70 years	No prevalence Penicillin	54 (96%) Type B reaction patients had negative skin testing and successful 3-day 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) [39] Australia (New South Wales)	Immunology and Infectious Diseases	Case Series	N = 149 patients enrolled through in-patient 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

Author Article, Year And Country	Leading Team	Study Design	Sample size/ Participants	Prevalence/type of Reported AAL	Key Results	Intervention
Livirya *et al*. (2022) [45] New Zealand (Hastings)	Infectious Diseases and Immunology	Case Series	N = 224 patients identified with an active antibiotic allergy record. Mean Age: 73 years	16% Penicillin	162 patients were deemed low risk. Of these 56 had tolerated penicillin antibiotics since the index reaction and were de-labelled without challenge together with a further 15 with a non-allergic history. 41 were challenged without issue. Of the original 224 patients screened, 50% were successfully de-labelled.	Direct oral provocation challenge.
Lucas *et al.* (2018) [4] Australia (Western Australia)	Immunology	Retrospective Cohort Study	N = 1672 patients admitted to a tertiary children's hospital over a one year period Age: 0-18 years	5% All Antibiotics	Prevalence of antibiotic allergy increased with age. Oncology or other specialities were more likely to have AALs than those in general medical or surgical. AALs 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 years	19% Beta-lactam	35% of AAL patients did not receive the preferred beta lactam therapy due to their reported allergy. These patients are significantly more likely to experience an adverse event.	None
Macy E, & Shu Y, (2017) [28] USA (California)		Cohort Study	N = 308 matched to 1251 control patients who were penicillin allergic attending outpatient services. Median Age: 35-39 years	No prevalence Penicillin	Case subjects had significantly fewer OPD follow up visits, hospital days and ED presentation in the four year follow up period that 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.
Mason *et al.* (2019) [29] USA (New York)		Prospective Cohort Study	N = 1844 identified through electronic alert, prescribed antibiotics. Mean Age: 32 years	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 day readmission/retreatment rates.	None

Author Article, Year And Country	Leading Team	Study Design	Sample size/ Participants	Prevalence/type of Reported AAL	Key Results	Intervention
Modi *et al.* (2019) [30] USA (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 years	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 was noted with a reduced incidence of *C.diff.* There were not differences in length of stay, ICU admissions or mortality.	SPT/IDT testing and graded oral challenge.
Perez-Encinas *et al*. (2021) [47] Spain (Madrid)		Retrospective Cohort Study	N = 931,291 patients discharged from the Spanish hospital system Median Age: 63-70 years	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] USA (Florida)		Retrospective Cohort Study	N = 280 patients admitted with a reported penicillin allergy to a community teaching hospital Mean Age: 60-65 years	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.* (2021) [19] United Kingdom (Cornwall)		Retrospective Cohort Study	N = 23,356 inpatients Age: 0-103 years	14% Penicillin	AAL's more likely to be female, older and have more co-morbidities. 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.* (2021) [31] USA (North Carolina)		Retrospective Cohort Study	N = 39,972 patients undergoing surgery at three hospitals between 2013-2017. 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.* (2020) [32] USA (New York)	Pharmacist	Retrospective Cohort Study	N = 32 patients admitted with a reported penicillin allergy Median Age: 57 years	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

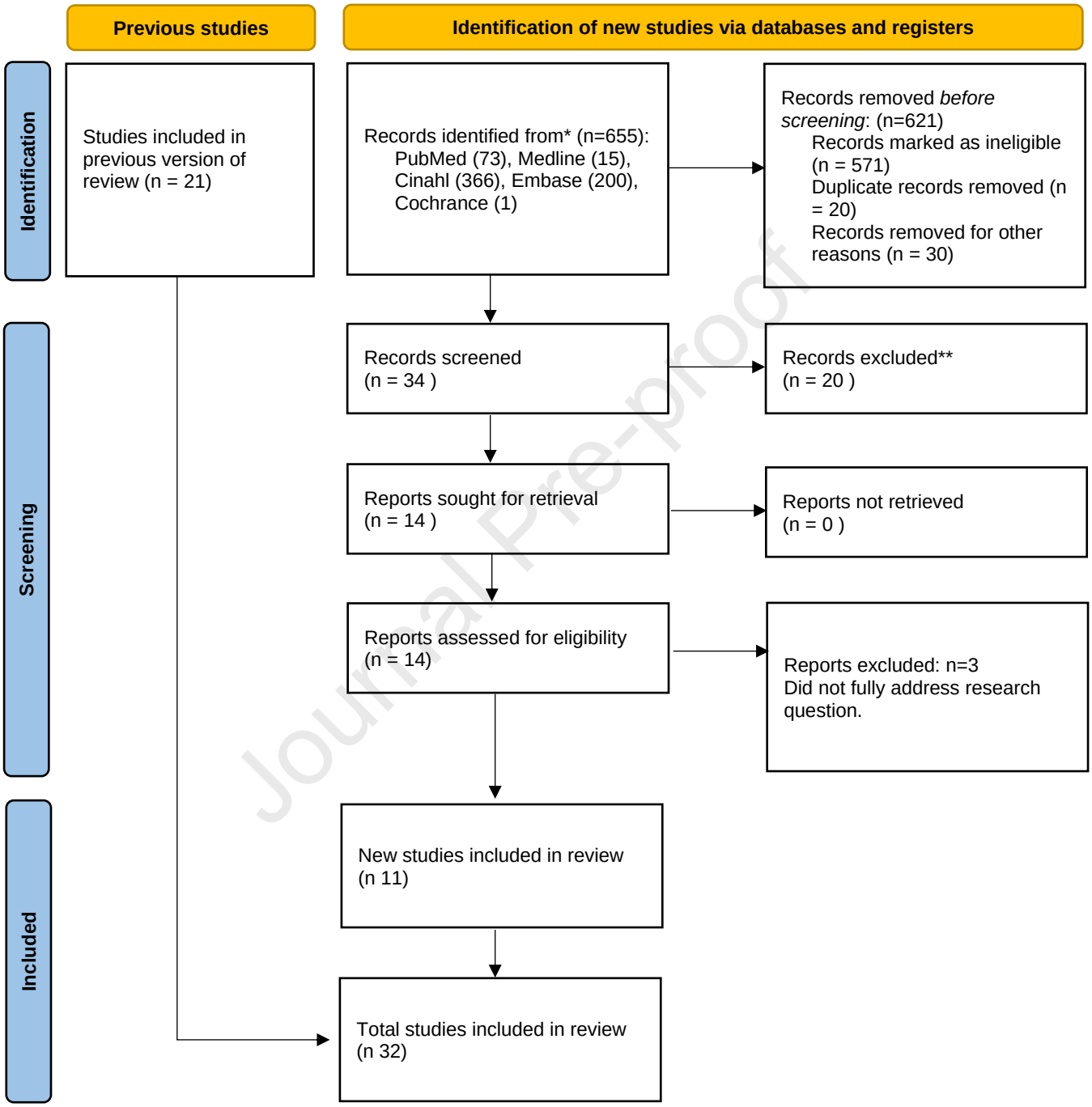
Author Article, Year And Country	Leading Team	Study Design	Sample size/ Participants	Prevalence/type of Reported AAL	Key Results	Intervention
Steenvoorden *et al.* (2021) [48] Norway (Oslo)	General Medicine	Case Series	N = 257 of patients admitted with a reported penicillin allergy. Mean Age: 68-74 years	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 hospitalised patients.
Swearingen *et al.* (2016) [33] USA (Pennsylvania)		Cohort Study	N = 211 admitted to an academic teaching hospital Mean Age: 65-65 years	No prevalence Penicillin	Post intervention there was a statistically significant decrease in the use a 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 two groups. 83% of patients in the post intervention group had there 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) [34] USA (Texas)	Infectious Diseases	Cohort Study	N = 100 admitted to a cancer centre with a reported penicillin allergy Median Age: 65 years	No prevalence Penicillin	95% of patients who underwent skin testing and oral challenge tested negative for penicillin allergy. Skin testing and oral challenge is 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) [40] Australia (Victoria)	Infectious Diseases	Prospective Cohort Study	N = 198 patients admitted to a tertiary cancer unit Median Age: 64-65 years	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 non-allergy group	

Author Article, Year And Country		Study Design	Sample size/ Participants	Prevalence/type of Reported AAL	Key Results	Intervention
Trubiano *et al.* (2015) [41] Australia (Victoria)	Infectious Diseases	Cohort Study	N = 509 patients admitted under antimicrobial stewardship Median Age: 58-59 years	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 re-admission rate for allergy group.	None
Trubiano *et al.* (2016) [42] Australia (Victoria)	Infectious Diseases	Cohort Study	N = 21031 patients captured on the NAPS receiving antimicrobials Median Age: 66 years	18% All Antibiotics	AALs are associated with inappropriate and excess antimicrobial prescribing. A higher proportion of AAL patients had more than one non-compliant 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) [43] Australia (Victoria0	Infectious Diseases	Cohort Study	N = 118 patients referred to two tertiary cancer care units Median Age: 59 years	No prevalence Beta-lactam	Evidence that the integration of Antibiotic Allergy Testing into Antimicrobial Stewardship Programmes 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 day extended course
Van Dijk *et al.* (2016) [49]		Matched Cohort Study	N =17959 admitted to a Dutch Medical Centre over a one-year period Median Age: 55 years	6% Penicillin	Patients in the allergy group were significantly more likely to receive reserve antibiotics and were more likely to be re-hospitalised within 12 weeks of admission.	None

Table 2.

Author and Year	Alternative antimicrobial Prescribing	Increase in Length of Stay	Increase in Re-admission	Longer duration of therapy	Increase in microbial resistance
Catalano *et al.* (2021) [35]	✓	✓	-	-	-
Chakravorty *et al.* (2022) [36]	✓	-	-	-	✓
Conway *et al.* (2017) [2]	✓	-	-	-	-
Gulholm *et al.* (2021) [38]	✓	-	-	-	-
Huang *et al.* (2018) [26]	-	✓	✓	-	✓
Jones *et al.*[27]	✓	-	-	-	-
Knezevic *et al* (2018) [7]	✓	-	✓	-	-
Lucas *et al.* (2018).[4]	✓	✓	-	-	-
MacFadden *et al.* (2016).[6]	✓	-	-	-	-
Mason *et al.* (2019).[29]	✓	-	-	-	-
Perez-Encinas *et al* (2021) [47]	-	✓	-	-	-
Powell *et al.* (2021) [19]	✓	-	-	-	-
Seidelman *et al.* (2021) [31]		-	-	✓	-
Trubiano *et al.* (2015) [40]	✓	-	-	✓	-
Trubiano *et al.* (2015). [41]	-	-	✓	✓	-
Trubiano *et al.* (2016). [42]	-	-	-	-	-
Van Dijk *et al.* (2016). [49]	✓	-	✓	-	-

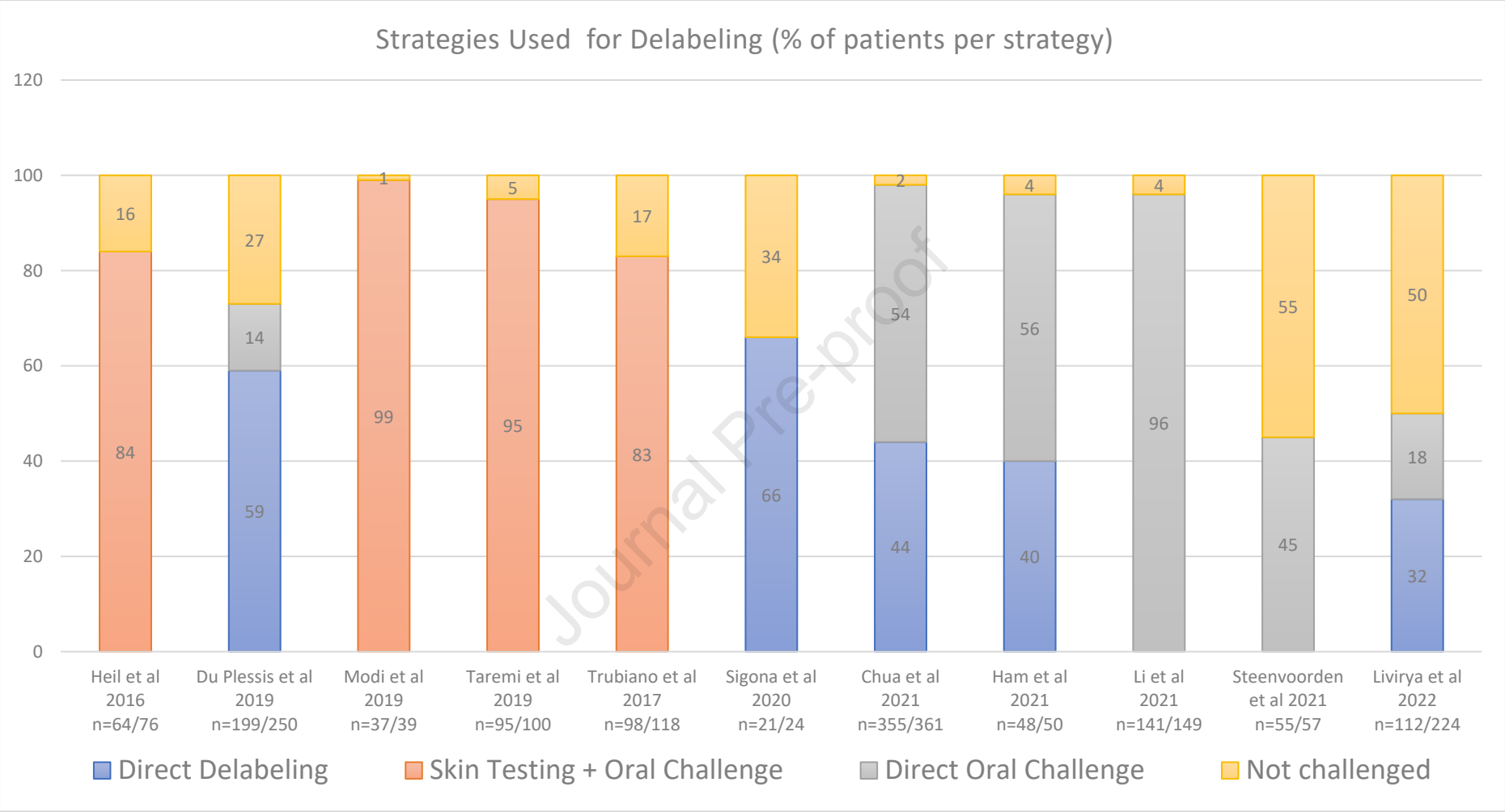
Figure 1.



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Figure 2.



n=delabeled/total challenged

Supplemental Information Figure and Table Legends

Figure E1

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]
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cephalosporin allerg*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
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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

Cochrane Library

(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

Medline

antimicrobial stewardship.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
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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

Population	**Intervention**	**Comparison**	**Outcome**
Patients with Reported Penicillin Allergy	**Antimicrobial Stewardship Programme**	**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			Re-admission rates
MH Beta Lactams			Intensive care admissions
MH Penicillins			Mortality
			MH intensive care units
			MH Intensive care
			MH Drug resistance, microbial
			MH Mortality

PICO Framework (Ericksen and Frandsen, 2018)

Table E2

Critical appraisal table for cohort studies without an intervention (n=15)

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Total # 'Yes'
Conway et al[13]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	n/a	10
Catalano et al[16]	Y	Y	Y	N	N	Y	Y	Y	n/a	n/a	Y	7
Chakravorty et al[12]	Y	Y	Y	Y	Y	Y	Y	Y	n/a	n/a	Y	9
Huang et al[40]	Y	Y	Y	Y	Y	Y	Y	Y	Y	n/a	Y	10
Jones et al[3]	Y	Y	Y	Y	Y	U	Y	Y	Y	n/a	n/a	8
Knezevic et al	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11
Lucas et al[57]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11
MacFadden et al[58]	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	9
Mason et al[63]	Y	Y	Y	Y	Y	Y	Y	Y	Y	n/a	Y	10
Perez et al[36]	Y	Y	Y	Y	Y	Y	Y	Y	Y	n/a	Y	10
Powell et al[4]	Y	Y	Y	Y	Y	Y	Y	Y	n/a	n/a	n/a	8
Seidelman et al[31]	Y	Y	Y	Y	Y	U	Y	n/a	n/a	n/a	Y	7
Trubiano et al[97]	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	9
Trubiano et al[100]	Y	Y	Y	Y	Y	Y	Y	Y	Y	n/a	Y	10
Trubiano et al[103]	Y	Y	Y	N	Y	Y	Y	Y	Y	n/a	Y	9
Van Dijk et al[108]	Y	Y	Y	U	U	Y	Y	Y	Y	n/a	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 to 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[21]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	9
Heil et al[36]	Y	Y	Y	N	N	Y	Y	Y	N	N	Y	7
Li et al[52]	Y	Y	Y	N	N	Y	Y	Y	N	N	Y	7
Phan et al[75]	Y	Y	Y	Y	N	N	Y	Y	N	N	Y	7
Macy & Shu[60]	Y	Y	Y	Y	Y	Y	Y	Y	Y	n/a	Y	10
Modi et al[67]	Y	Y	Y	Y	U	Y	Y	Y	Y	n/a	Y	9
Sigona et al[87]	U	U	Y	U	U	Y	Y	U	Y	n/a	Y	5
Swearingham et al[91]	Y	Y	Y	N	N	N	Y	Y	N	N	Y	6
Taremi et al[92]	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y	8
Trubiano et al[104]	Y	Y	Y	N	n/a	Y	Y	Y	Y	n/a	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 to 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[32]	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[6]	Y	Y	Y	N	N	Y	Y	Y	N	U	6
Li et al[22]	Y	Y	Y	Y	U	Y	Y	Y	N	U	7
Livirya et al[23]	Y	Y	Y	U	Y	Y	Y	Y	Y	U	8
Steenvoorden et al[29]	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[2]	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' (i.e. 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 two groups in terms of their follow up adequately described and analysed?; 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?.