Safety and efficacy of de-labelling penicillin allergy in adults using direct oral challenge: a systematic review

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Background: Approximately 10% of people have an unverified penicillin allergy, with multiple personal and public health consequences.

Objectives: To assess the efficacy and safety of direct oral challenge, without prior skin testing, in this population.

Methods: MEDLINE, EMBASE, CINAHL, the Cochrane Library and Google Scholar were searched from inception to 28 June 2020 (updated November 2020) to find published and unpublished studies that reported direct oral challenge for the purpose of removal of penicillin allergy labels. Population weighted mean was used to calculate the proportion of patients who developed an immediate or delayed reaction to direct oral challenge across the studies.

Results: Thirteen studies were included in the review, with a sample size of 1202 (range 7–328). Studies included inpatient and outpatient cohorts assessed as low risk for true allergy. In pooled analysis of all 13 studies there were 41/1202 (3.41%) mild immediate or delayed reactions to direct oral challenge. The population-weighted mean incidence of immediate or delayed reaction to an oral challenge across studies was also 3.41% (95% CI: 2.38%–4.43%). There were no reports of serious adverse reactions, 96.5% of patients could be de-labelled and many were subsequently successfully treated with penicillin.

Conclusions: Direct oral challenge is safe and effective for de-labelling patients assessed as low risk for true allergy. Non-specialist clinicians competent in using an assessment algorithm can offer evaluation of penicillin allergy labels using direct oral challenge in appropriate patients. These measures will facilitate optimal infection treatment for patients, support antimicrobial stewardship, and minimize antimicrobial resistance.

Introduction

Approximately 10% of people carry an unverified penicillin allergy label on their medical record. However, the true prevalence of penicillin hypersensitivity reaction based on allergy history is unknown.1,2 It is likely that only 10%–20% of self-reported penicillin allergies will be confirmed with formal evaluation.3,4 Patients in hospital are particularly likely to report a penicillin allergy.1 Studies show that 35.7% and 50% of hospitalized patients in Scotland and the US, respectively, receive at least one course of antibiotic treatment during their admission.5,6 Therefore, it is important to ensure accuracy of a penicillin allergy label to prevent unnecessary penicillin avoidance and inappropriate use of alternative non-β-lactam antibiotics which may be less effective.7 Injudicious use of alternative broad-spectrum antibiotics is associated with increased direct costs to the healthcare service, longer duration of patient stay in hospital, increased risk of adverse effects, and development of antimicrobial resistance (AMR).7–11

Oral challenge (OC) is deemed the gold standard test for the removal or verification of penicillin allergy, as skin and in vitro tests do not demonstrate 100% sensitivity or specificity.12 Assessment of penicillin allergy is usually carried out by allergy specialists starting with skin prick testing (SPT) and intradermal testing (IDT). These procedures are time-consuming and expensive, furthermore, specialist allergy assessment services are not widely available across the UK.13
Recent studies have shown that patients’ risk of true allergy can be assessed using a decision algorithm and those deemed low risk can be offered a direct oral challenge with low incidence of adverse events. The objective of this review was to assess the safety (i.e. number of people who experience a reaction) and efficacy of direct oral challenge with amoxicillin or the culprit penicillin for supporting de-labelling in adults with an unverified penicillin allergy label.

Methods

This systematic review is reported in accordance with the Joanna Briggs Institute (JBI) Reviewers Manual. The objectives, inclusion criteria and methods of analysis were specified in advance and published in a protocol (PROSPERO CRD42020176432).

Inclusion/exclusion criteria

Studies that met the following criteria were included in the systematic review: (i) adult inpatients or outpatients with a documented penicillin allergy on their medical record; (ii) objectively or subjectively reported reactions to direct oral challenge with amoxicillin or the culprit penicillin to rule out or confirm allergy; (iii) reported subsequent treatment of infection with a penicillin after direct oral challenge, including adverse events associated with treatment; (iv) any study design; and (v) studies that reported SPT/IDT prior to direct OC were excluded, even if results were ignored.

Search strategy

An initial limited search of Ovid MEDLINE and Ovid EMBASE was undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the articles. A second search using all identified keywords and index terms was then undertaken using the following databases: the Cochrane Library, CINHAL, Ovid EMBASE, Ovid MEDLINE and Google Scholar, from inception to 28 June 2020. The Ovid MEDLINE search was updated on the 2 November 2020. The search strategy was reviewed by an experienced librarian. Search terms included index terms as well as keywords for the concepts penicillin, penicillin allergy, reaction, hypersensitivity, de-labelling, provocation testing, and oral challenge (the full search strategy is provided as Supplementary data at JAC-AMR Online). Reference lists of included publications were checked for additional relevant studies. Following removal of duplicates, all titles and abstracts were screened by two authors (L.C. and J.H.). Disagreements were resolved by consensus or by discussion with a third author if required. Full text was retrieved for all records deemed to meet the inclusion criteria.

Assessment of methodological quality

Studies selected for critical appraisal were assessed independently by two authors (L.C. and J.H.) using standardized critical appraisal instruments from the JBI. Disagreements were resolved by consensus or by discussion with a third author if required.

Data extraction

Two authors (L.C. and J.H.) independently extracted data using a standardized data extraction tool. The data extracted included study design,
setting and sample size, criteria used to define low risk of true allergy, details about the direct oral challenge method, duration of challenge and follow-up, number of patients showing an immediate or delayed allergy response, number of patients de-labelled, and subsequent treatment with penicillin (including any delayed reactions to penicillin).

Data synthesis

The primary statistic extracted from each study was the number of participants who developed any immediate or delayed reaction to the OC. Population-weighted analysis was conducted on individual studies reporting the rate of positive direct OCs to produce a population weighted mean. The 95% confidence interval (CI) was calculated using Excel.

Results

Following removal of duplicates and addition of one study found by checking references, a total of 804 citations were identified. Review of titles and abstracts led to the full text for 36 potentially relevant papers being obtained and evaluated against the inclusion criteria by L.C. and J.H. Twenty-three publications were excluded at this stage, resulting in 13 studies being included in the systematic review. Figure 1 details the study selection flow chart presented according to the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines.19

Methodological quality

The results of the critical appraisal of included studies are presented in Tables 1 and 2. Twelve observational studies and one randomized clinical trial (RCT) were critically appraised and included in the review. Overall median quality score was 6/8 (range 4–8) for observational studies and 6/13 for the RCT.

Description of studies

A summary of included studies (n = 13) is presented in Table 3. This systematic review included one RCT,20 nine prospective observational studies21–29 and three retrospective observational studies,30–32 with a total of 1202 participants. There was considerable variation in the number of participants in individual studies, with a median of 47 participants (range 7–328). Studies investigated the safety and effectiveness of direct oral challenge with culprit penicillin or amoxicillin in participants with a documented penicillin allergy label. The RCT compared skin prick test plus OC versus OC only.20 The clinical settings for included studies were outpatient clinics (n = 5),20,22,27,31,32 inpatient facilities (n = 7),21,23–26,28,29 and a Marine recruit assessment centre.30 Studies were conducted in the US (n = 6),20,22,25,26,30,31 Australia (n = 5),21,23,28,29,32 the Netherlands (n = 1),24 and the UK (n = 1).27

The study in a Marine recruit assessment centre included only male patients aged typically between 18 and 25 years,30 the

Table 1. Critical appraisal of observational studies

| Question | Savic 201927 | Devchand 201921 | Ramsey 202016 | Iammatteo 201922 | du Plessis 201925 | Trubiano 201828 | Li 201923 | Stevenson 202012 | Lin 202024 | Tucker 201730 | Kuruvilla 201931 | Chua 202039 |
|----------|-------------|----------------|-------------|-----------------|------------------|----------------|--------|-----------------|-------------|------------|----------------|-------------|
| 1. Were the criteria for inclusion in the sample clearly defined? | Y | Y | Y | Y | Y | Y | UC | Y | Y | Y | Y | Y |
| 2. Were the study subjects and the setting described in detail? | N | Y | Y | Y | Y | Y | Y | Y | N | Y | Y |
| 3. Was the exposure measured in a valid and reliable way? | Y | UC | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 4. Were objective, standard criteria used for measurement of the condition? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 5. Were confounding factors stated? | NA | NA | NA | UC | NA | NA | NA | Y | NA | NA | NA | NA |
| 6. Were strategies to deal with confounding factors stated? | NA | NA | NA | N | NA | NA | NA | Y | NA | NA | NA | NA |
| 7. Were outcomes measured in a valid and reliable way? | Y | Y | Y | Y | UC | Y | Y | Y | Y | Y | Y | Y |
| 8. Was appropriate statistical analysis used? | UC | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | NA | Y |

Legend: Y, yes; N, no; NA, not applicable; UC, unclear.

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remaining studies reported a higher proportion of female patients ranging from 51.4%–77.4%. The mean age of study participants ranged from 35.3–70.4 years. Two studies had inclusion criteria that allowed for patients aged 16 years or older.23,32 One study reported that a validated tool was used;21,28,29 other tools had been developed from previously published work or specifically for the study. Two studies reported review of clinical history only, however these studies were conducted by allergy specialists.23,30 Studies reported that participants were monitored for at least 30 min between doses in multi-step oral challenges,20,22,23,25–27,32 and for between 1 and 2 h after administration of a full single dose.26,28,29,31 Patients were contacted by the research team, usually within 1–4 weeks of the oral challenge, or instructed to make contact if a delayed reaction to the challenge drug occurred.22,26–28,32 Longer-term follow-up at 90 days28 and 1 year21,26 was reported in three studies to determine subsequent use of penicillin-based antibiotics. Researchers contacted patients’ general practitioners in two studies to confirm that medical records were updated to reflect the patient’s updated allergy status.73,27

Findings of the review

Primary outcome: response to direct oral challenge

The main clinical outcome reported in included studies was the ability to remove the penicillin allergy label from the medical records of patients who had no reaction to direct OC with culprit penicillin or amoxicillin. Figure 2 shows the percentage of patients in individual studies who reacted to direct OC along with the population-weighted mean for all studies. Overall, 1202 patients were assessed as low risk and proceeded to a supervised oral challenge with penicillin. One study reported that 20% of patients experienced a non-allergic reaction to the placebo or amoxicillin.27 Of the 1202 patients challenged, a total of 41 patients (3.41%) experienced a reaction to direct OC, of which 17 (41%) reactions were immediate and 24 (59%) were delayed reactions to direct OC. All reactions were reported as mild or intermediate. Three studies reported treatment for reactions; Immatteo et al.22 reported that one patient who required treatment with antihistamines for a non-immediate rash had resolution within 24 h and one patient with intractable pruritus determined to be an allergy had resolution within 1 h of antihistamine treatment, Ramsay et al.26 reported that one patient with mild swelling and redness under the eyes was treated with oral diphenhydramine while Tucker et al.30 reported treating four isolated cutaneous reactions and one globus reaction with oral antihistamine—participants were also given a single intramuscular dose of epinephrine to avoid reaction progression. There were no reported cases of serious adverse reactions or anaphylaxis in any study and 96.5% of challenged patients could be de-labelled. The proportion of patients who experienced a reaction to direct OC in individual studies ranged between 0% and 15%. The population-weighted mean proportion of patients across all 13 studies who had an immediate or delayed reaction following direct OC was 3.41%, (95% CI: 2.38%–4.43%) (Figure 2).

The patients randomized to receive direct OC in the RCT were included in the pooled analysis as an outpatient cohort.20 In the RCT, 379 (3.8%) patients randomized to direct OC had a reaction, compared with 10/80 (12.5%) patients randomized to SPT plus OC who reported a positive SPT. Participants in the direct OC

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**Table 2. Critical appraisal of randomized clinical trials**

| Question | Mustafa 201920 |
|----------|----------------|
| 1. Was true randomization used for assignment of participants to treatment groups? | N |
| 2. Was allocation to treatment groups concealed? | N |
| 3. Were treatment groups similar at baseline? | Y |
| 4. Were participants blind to treatment assignment? | N |
| 5. Were those delivering treatment blind to treatment assignment? | N |
| 6. Were outcomes assessors blind to treatment assignment? | N |
| 7. Were treatment groups treated identically other than the intervention of interest? | UC |
| 8. Was follow-up complete and if not, were differences between groups in terms of their follow up adequately described and analysed? | Y |
| 9. Were participants analysed in the groups to which they were randomized? | Y |
| 10. Were outcomes measured in the same way for treatment groups? | Y |
| 11. Were outcomes measured in a reliable way? | Y |
| 12. Was appropriate statistical analysis used? | Y |
| 13. Was the trial design appropriate, and any deviations from the standard RCT designed account for in the conduct and analysis of the trial? | N |

Legend: Y, yes; N, no; NA, not applicable; UC, unclear. Questions are reproduced with kind permission from the Joanna Briggs Institute (JBI) from their critical appraisal tools (https://joannabriggs.org/critical-appraisal-tools).
| Study                        | Clinical setting/country | Sample size | Low risk criteria/assessment tool used | Type of challenge                                                                 | Length of observation/follow-up                                                                 | Staff involved                                                                 | Results                                                                                                                                                                                                 |
|-----------------------------|--------------------------|-------------|----------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Savic et al. (2019)²⁷       | Dedicated de-labelling clinic UK | 56          | Low risk symptoms (nausea, vomiting, diarrhoea, non-itchy rash, thrush, not admitted to hospital, do not know/cannot remember) | Amoxicillin 500 mg in incremental doses 10%, 50% and 100% 3 day course of antibiotics to complete at home | 20 min intervals between doses and 1 h after full dose in clinic Phone call at end of course (5–7 days after clinic) | Screened by nurses trained to undertake screening                                       | One patient developed urticaria in hands after 2nd dose and stopped. 4 patients mild non-allergic symptoms during prolonged course (sore throat, cough, worsening arthralgia and mild nausea in 2) 17/19 had penicillin-based SAP. Correct allergy status confirmed by GP for 47/55 patients |
| Devchand et al. (2019)²¹   | General wards Australia  | 20          | Childhood exanthem, details of rash timing unknown and no severe features or hospitalization Delayed hypersensitivity rash >10 years ago Unknown reaction or family history of penicillin allergy only Validated assessment tool used | Inpatient DOC administered by trained allergy nurse Dose and type of drug not reported | Not reported                                                                                   | Screened by AMS pharmacist Reviewed on ward round by ID consultant, allergy nurse and AMS pharmacist Administered by allergy nurse | 1/20 experienced delayed rash post-discharge. Label reapplied 18/20 patients prescribed penicillin during current admission. 10/20 (50%) prescribed restricted antibiotic before challenge vs 4/20 (20%) after ($P = 0.0958$) |
| Ramsey et al. (2020)²⁶     | Medical wards US         | 48          | Cutaneous-only reaction (non-specific rash, itching, or urticaria) Unknown reaction history of >20 years ago No need for medical attention Algorithm developed from previously published work | 3 step direct challenge 1/100th full dose, 1/10th full dose, full dose | 30 min separation between doses Follow-up call 2 weeks later | Screened by ID PharmD Evaluated by allergist Administered by nurse in usual ward | 1/48 immediate mild reaction after step 2 2/48 (4.2%) experienced delayed reaction.                                                                                                                                 |
| Iammateo et al. (2019)²²   | Outpatient drug allergy clinic US | 155         | Non-life threatening reactions Decision support tool | Patients challenged with placebo followed by a 2-step oral graded | 30 min observation following placebo + 30 min observation following 1st dose + 60 min observation | Screened by allergy clinic staff Administered by allergy clinic staffed | 16 non allergic reaction to placebo 15 non allergic reaction to amoxicillin.                                                                                                                                 |

Continued
Table 3.  
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| Study | Clinical setting/country | Sample size | Low risk criteria/assessment tool used | Type of challenge | Length of observation/follow-up | Staff involved | Results |
|-------|--------------------------|-------------|---------------------------------------|-------------------|---------------------------------|---------------|---------|
| Kuruvilla et al. (2019) | Outpatient allergy clinic | 20 | History of benign rash, benign somatic symptoms or unknown history associated with last penicillin exposure > 12 months ago | Amoxicillin 500 mg single dose | Monitored for 60 min after challenge. Vital signs at baseline and every 30 min. Advised to call if delayed reaction occurred. | Assessed by allergist | 3/20 self-limited subjective symptoms |
| Mustafa et al. (2019) | Outpatient allergy practice | 159 | Cutaneous-only reaction >10 years ago | 80 SPT followed by oral amoxicillin challenge 79 2-step DOC 1/10th dose amoxicillin followed by full dose | Monitored for 30 min following 1st dose and 30 min following 2nd dose | Assessed by allergist | 10/80 had positive skin test 3/79 had positive DOC—no systemic reactions in either group 8.7% fewer positive evaluations compared with skin test P = 0.079 |
| du Plessis et al. (2019) | General wards | 34 | Delayed onset rash >5 years ago | Placebo, Placebo, amoxicillin 5 mg, 50 mg then 500 mg | Patients observed for 30 min between doses Followed up 1 month and 1 year | Screening, assessment and challenge conducted by specially trained pharmacist Screened by antibiotic allergy nurse or ID physician Allergy service Nurse supervised challenge | 3 (3.8%) positive reaction within 72 h. no hypersensitivity reaction |
| Trubiano et al. (2018) | Hospital inpatients and outpatients | 46 | Unknown reaction >10 years ago or date cannot be recalled Type A adverse reaction Maculopapular exanthem >10 years ago or isolated non-urticarial rash or benign childhood rash Validated assessment tool | Penicillin VK 250 mg or amoxicillin 250 mg based on implicated drug Patients with history of delayed hypersensitivity were given 5-day challenge with same drug | Patients observed for 2 h following administration of drug. | Screened by antibiotic allergy nurse or ID physician Allergy service Nurse supervised challenge | No adverse reactions reported |
| Study | Design | Setting | Participants | Clinical History | Observation Period | Challenge Administration | Methodology |
|-------|--------|---------|--------------|------------------|--------------------|------------------------|-------------|
| Li et al. (2019) | Prospective single-centre clinical case series with retrospective control group | General wards | General wards | 7 | Type A reaction (nausea, abdominal pain, vomiting, diarrhoea) | 3 day course of amoxicillin | 30 min observation after each dose until final dose then 2 h observation. | Assessed by allergist and allergy nurse or registrar |
| Stevenson et al. (2020) | Retrospective multi-centre cohort study | Hospital immunology outpatient clinics | Australia | 7 | Benign immediate or delayed rash (without mucosal involvement) >1 year ago identified as optimal definition of low risk | 1 or 2 doses e.g. 1/10, full dose amoxicillin or culprit drug if known | Minimum 30 min observation between doses and 1 h after the final dose. Telephone follow-up 3 to 7 days | Challenge administered by staff trained to manage anaphylaxis |
| Lin et al. (2020) | Prospective single-centre cohort study | General wards | Netherlands | 42 | Delayed onset of rash, rhinitis, gastrointestinal symptoms >12 months ago or ≤2 symptoms considered moderate risk (e.g. urticaria, oedema, mild dyspnoea, fever, indication for hospitalization) | DOC 500 mg amoxicillin or 500 mg/125 mg amoxicillin-clavulanic acid depending on preferred treatment. | 60 min observation following administration | Screened by treatment physician or pharmacist assistant. Medical supervision of challenge |
| Tucker et al. (2017) | Retrospective chart review | Marine recruit depot | US | 328 | Low risk not defined. Exclusion criteria defined as serious cutaneous reactions | 250 mg amoxicillin | Not reported | Assessed and challenged by allergist/medical centre staff |
| Chua et al. (2020) | Prospective 2 centre study | General and cancer wards | Australia | 200 | Unknown reaction >10 years ago Type A adverse drug reaction (where direct delabelling not accepted by patient) | 250 mg penicillin VK or 250 mg amoxicillin | 2 h | Screened and assessed by trained nurses, pharmacist or medical staff |

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group experienced 8.7% fewer positive results than those randomized to the SPT plus OC group \((P = 0.079)\). In addition, four studies reported that patients assessed as very low risk were directly delabelled.\(^{21,22,25,29}\) In seven studies, inpatients who required antibiotics for surgical prophylaxis or treatment of an infection where penicillin was the preferred option were switched to penicillin immediately or prescribed penicillin after the direct oral challenge.\(^{21,24–29}\) Three studies reported that patients who had subsequently completed treatment with penicillin sometime after the challenge experienced either no adverse effects or only mild, delayed symptoms that self-resolved and did not preclude the completion of treatment.\(^{22,26,30}\) The penicillin allergy label was reported as removed from patients’ electronic medical record.\(^{21,30}\) In one study participants’ GPs confirmed that 47/55 (85%) patients had the correct revised allergy status recorded on their medical files,\(^{27}\) however in another study only 33% of patient medical records had been updated to reflect the correct allergy status.\(^{23}\)

**Discussion**

The aim of this review was to investigate the safety and efficacy of direct OC for the removal of an unverified penicillin allergy label. Analysis of the studies included in the review demonstrates that in patients assessed as having a low risk of true allergy to penicillin, based on their allergy history, direct oral challenge can be carried out safely and is effective for de-labelling patients with unverified allergy labels. Two earlier reviews support the need for non-specialist evaluation of penicillin allergy and the safety of direct OC in low-risk individuals.\(^{2,15}\)

Use of a structured process or algorithm to standardize how an allergy history was taken was a key component of assessment by both allergists and non-specialists in most of the included studies. Clear guidelines, validated tools and training of generalist care providers in accurately assessing patients’ allergy history is essential to ensure patient safety during direct OC.\(^{33}\) It should be noted that only patients who were assessed as low risk according to individual study criteria were offered direct OC. Those who reported a recent allergy reaction and those reporting serious symptoms associated with IgE-mediated hypersensitivity were deemed high risk and direct OC was not offered. This group of patients were advised to continue to avoid using penicillin or referred for specialist allergy assessment. In addition to reducing the need for specialist input, using direct OC to remove an unverified penicillin allergy label requires less staff and patient time, and less equipment, than SPT or IDT, making it less expensive overall.\(^{26,34}\) Studies in this review have also demonstrated that with the correct training in assessment and administration processes, direct OC could be delivered in non-specialist settings. Given that four studies reported that very low-risk patients were de-labelled based on history alone,\(^{21}\) it may be prudent to include training on direct de-labelling for non-specialists.

Multiple benefits are derived from removal of an inappropriate penicillin allergy label. The most commonly reported clinical benefit is a change of antibiotic therapy,\(^{21,24–29,35}\) thus where a β-lactam is the preferred treatment patients are more likely to receive the most appropriate therapy,\(^{33,36,37}\) which in turn reduces inappropriate use of antibiotics classified as Watch or Reserve by the World Health Organisation.\(^{38}\)
Decreased use of broad-spectrum non-penicillin antibiotics reduces direct drug costs \textsuperscript{25,26,37,39} and length of hospital stay, with an associated reduction in healthcare costs. \textsuperscript{11,25} A recent study in the UK estimated that de-labelling 50\% of patients with a self-reported penicillin allergy would save £5501 in antibiotic drug costs and £503 932 in reduced excess bed days annually in one large hospital. \textsuperscript{13} Long-term follow-up to determine accurate update of patient records and patient understanding of de-labelling is also important to ensure patients continue to receive optimal antibiotic treatment. \textsuperscript{40}

Eleven of the studies in this review used a standardized questionnaire or screening tool to assess the patients’ history to determine risk of true allergy. The two studies that assessed patients on clinical history alone were carried out by allergy specialists. While elements of the tools were similar across the studies, only three were reported as validated. Devchand \textit{et al.} \textsuperscript{41} recently validated a tool designed to be used by non-specialist clinicians to assign an accurate phenotype and management strategy for patients reporting penicillin allergy. Adoption of a validated tool and provision of appropriate training could increase the confidence of non-specialist clinicians in assessing, testing and de-labelling patients with unverified penicillin allergy, which will contribute to antimicrobial stewardship.

The inclusion of only one RCT could be considered a limitation of this review, therefore further RCTs are required to demonstrate the safety of de-labelling with direct OC in low-risk patients. The majority of included studies were single-arm observational studies, which prevented assessment of the comparative safety of direct OC for de-labelling penicillin allergy. Six of the included studies were conducted by allergists, thus perhaps limiting replication of these results by non-allergy specialist clinicians, therefore future studies with direct OC conducted by non-specialists should be considered. Additional limitations concerning the review process include the language restriction to papers in English, the validity of pooling studies conducted in different settings and patient groups, or using different methods of direct oral challenge and combining subjective and objective measures of reactions.

Further longitudinal studies should be carried out to address the effects of de-labelling on subsequent use of antibiotics, allergy status documentation, hospital admissions and associated costs.

**Conclusions**

Patients with an unverified penicillin allergy should be investigated, especially those who require (or are likely to require) treatment with an antibiotic. Following careful screening using a standardized approach by trained (non-allergy specialist) clinicians, patients deemed at low risk of true allergy to penicillin can safely be offered direct OC and effectively de-labelled if appropriate. Non-specialist clinicians should be empowered to safely undertake the assessment of patients to risk stratify those for whom direct OC is appropriate. These measures will support antimicrobial stewardship, facilitate optimal infection management, and support other efforts to reduce antimicrobial resistance.

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**Transparency declarations**

None to declare.

**Supplementary data**

The search strategy is available as Supplementary data at JAC-AMR Online.
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