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**Highlights**

- Penicillin allergy de-labelling by non-allergists is safe.
- Less intensive methods delabelled a smaller proportion of patients.
- Once patients were assessed as suitable for testing, rates of de-label were high.
- A diverse workforce engaged in de-labelling incorrect penicillin allergy records.
- Penicillin allergy de-labelling interventions are described.

Journal Pre-proof

**The effectiveness of interventions that support penicillin allergy assessment and de-labelling of adult and paediatric patients by non-allergy specialists: a systematic review and meta-analysis**

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Abstract

### **Introduction:**

Penicillin allergy records are often incorrect and may result in harm. We aimed to systematically review the effectiveness and safety of non-allergist healthcare worker delivery of penicillin allergy de-labelling (PADL).

### **Methods**

We searched EMBASE/ MEDLINE/ CINAHL (Ovid), PsycInfo, Web of Science and Cochrane CENTRAL from inception to 21/01/22, and unpublished studies and the grey literature. The proportion of penicillin allergic patients de-labelled and harmed was calculated using random effects models.

### **Findings**

Overall, 5019 patients were de-labelled. Using allergy history alone, 14% (95% CI, 9.0-21%) of 4350 assessed patients were de-labelled without reported harm. Direct drug provocation testing resulted in de-labelling 27%; (95% CI, 18-37%) of 4207 assessed patients. Of 1373 tested, 98% were de-labelled (95% CI, 97-99%), harm, none serious, was reported in 1% (95% CI, 0-2%). Using skin testing followed by drug provocation testing de-labelled 41% (95% CI, 24-59%) of 2890 assessed patients. Of 1294 tested patients 95.0% (95% CI, 90%-99%) were de-labelled, reported harm was low.( 0%; (95% CI 0%-1%).

### **Interpretation**

PADL by non-allergists is efficacious and safe. The proportion of assessed patients who can be de-labelled increases with complexity of testing method, but substantial numbers can be de-labelled without skin testing.

## Funding

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Keywords: “antimicrobial stewardship”; “penicillin allergy assessment” “penicillin allergy de-labelling”; “non-allergists”

## Introduction

Approximately 6% of the general population (West, Smith et al. 2019) and 15% of hospital inpatients have a record of penicillin allergy (penA). (Macy and Contreras 2014, Trubiano, Smibert et al. 2018, Powell, Honeyford et al. 2020) Penicillin-based antibiotics are first-line treatment for many infections but patients with penA labels are usually treated with second line antibiotics (Powell, Honeyford et al. 2020) which are often more costly, can be less effective in certain clinical circumstances, more toxic, and often broader spectrum, potentially increasing a patient’s risk of future infections with resistant bacteria. (Krah, Jones et al. 2021) More than 95% of individuals with a penA label can tolerate penicillin. (Shenoy, Macy et al. 2019, DesBiens, Scalia et al. 2020)

Assessment of patients with reported penAs has been the role of allergists, but allergy services are limited. (Krishna, Huissoon et al. 2017) Traditional penA testing requires skin

testing prior to drug provocation testing, which remains the main testing method in Europe, making penA testing resource intense.(Mirakian, Leech et al. 2015, Romano, Atanaskovic-Markovic et al. 2020) Direct drug provocation testing (DPT), an oral challenge test, in patients with a low risk allergy history is less resource intense. Two systematic reviews have confirmed the safety and efficacy of DPT (without prior skin testing) as a method of de-labelling adults, delivered both by allergists and non-allergists.(DesBiens, Scalia et al. 2020, Cooper, Harbour et al. 2021) Skin testing prior to DPT has also been successfully delivered by non-allergists.(Wall, Peters et al. 2004, Englert and Weeks 2019)

The American Academy of Allergy Asthma and Immunology with the Infectious Diseases Society of America wrote to the Centers for Medicare and Medicaid Services to urge US hospitals to include verification of penA as part of its mandatory antibiotic stewardship programs.(Immunology 2020) The World Health Organisation has since recommended antibiotic de-labelling as an effective antimicrobial stewardship strategy.(Europe 2021 ) Enablement of the wider healthcare workforce to de-label eligible patients is required to deliver penA assessment and de-labelling at scale. Understanding the wider frameworks that enable non-allergists to safely de-label is required, enabling development of effective interventions that facilitate penA de-labelling by non-allergy specialists.

We systematically reviewed the literature to determine the proportion of patients with a reported penA who were safely de-labelled by non-allergy healthcare workers (HCWs), categorising components of interventions using the Effective Practice and Organisation of Care (EPOC) taxonomy of health interventions,((EPOC) 2016) and report any measured antimicrobial stewardship and health-system impact.

## Methods

This systematic review and meta-analysis was conducted in accordance with the Joanna Briggs Institute (JBI) methodology for systematic reviews of effectiveness,(Tufanaru C 2020) and is reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist.(Liberati, Altman et al. 2009)

## Inclusion/exclusion criteria

(i) Any patient (adult/child) with a penA record, in any healthcare context; (ii) having undergone penicillin allergy de-labelling (PADL) using any method; (iii) by non-allergy specialists; defined as a medical professional whose primary specialisation is not in allergy, or who has not trained in allergy as part of their specialty.(Savic, Khan et al. 2019) (iv) penA assessment and de-labelling interventions delivered by immunologists, or allergy specialists were excluded. All study designs were included, except case reports.

## Search strategy

The following databases were searched from inception to 21/01/2022 (NP) EMBASE (Ovid), MEDLINE (Ovid), CINAHL (Ovid), PsycInfo, Web of Science and Cochrane CENTRAL as was the grey literature. Known experts in the topic were contacted to ensure we have not overlooked relevant literature. The search strategy was reviewed by an experienced information specialist (KO). Only studies published in English were included due to a lack of funding for translation services. (Appendix 1)

Titles and abstracts were screened by two independent reviewers (NP, SA, DK, RO, JS) against the inclusion criteria (RAYYAN software).(Ouzzani, Hammady et al. 2016) Full text citations were assessed against the inclusion criteria by two independent reviewers (NP, RO) using RAYYAN software.(Ouzzani, Hammady et al. 2016) (Appendix 2 & 3). Disagreements were resolved through discussion.

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Assessment of methodological quality

Eligible studies were critically appraised by two reviewers (NP, BK) using critical appraisal instruments from the JBI.(Tufanaru C 2020) Authors were contacted to request additional data, where required. Studies were not excluded on the grounds of their risk of bias.

Data extraction

Data were extracted by one reviewer (NP), using a purpose built extraction tool in Excel(Corporation 2018) and included study design, country, setting, population age, gender, inclusion criteria, exclusion criteria, allergy testing method(s), HCW(s) delivering PADL, components of the PADL interventions, details about education and training, number of assessed patients, number tested, number that experienced unintended harm, and any reported antibiotic stewardship or healthcare system impact. Extraction of data from seven studies (10%) was validated by a second reviewer. Intervention components were categorised using the EPOC taxonomy of health interventions, enabling grouping of health system interventions by conceptual or practical similarities.((EPOC) 2016) Studies that utilised a risk stratification protocol for allergy testing were categorised in the “packages of care” subcategory. Complex interventions were categorised into the “care pathways” subcategory.(Skivington, Matthews et al. 2021) Governance arrangements were categorised as “Authority and accountability for quality of practice”.

## Definitions

See appendix 4 for definitions for de-labelling, skin testing/ drug provocation testing (ST/DPT), direct drug provocation testing (DDPT) and direct de-labelling on history alone (DDL), successful de-label and definitions of harm.

#### Data analysis

Population-weighted proportional meta-analysis was conducted on studies with a low/moderate risk of bias to determine the proportion of participants successfully de-labelled and the proportion with a positive penA test by de-label method (DDL, DDPT and ST/DPT), using the R package meta v 5.2.0.(Schwarzer 2022) Statistical heterogeneity was assessed using Chi-square test (threshold  $P < 0.1$ ) and the  $I^2$  statistic ( $I^2$  values  $< 25\%$ ,  $25-75\%$  and  $> 75\%$  considered to represent low, moderate and high heterogeneity, respectively). Overall estimates were obtained using random effects models.(Tufanaru, Munn et al. 2015) A funnel plot was generated to assess publication bias with funnel plot asymmetry tested using the Egger test.(Egger, Smith et al. 1997) We used the studentized residual to identify studies that contributed most to heterogeneity.(Viechtbauer and Cheung 2010) Studies with z absolute values  $> 1.96$ (Viechtbauer and Cheung 2010) were excluded from the analysis to assess their influence on the overall estimates. The remaining data are presented in narrative form.

## Results

## Study inclusion

In total, 11,545 papers were identified, of which 3411 were excluded due to duplication.

Review of titles and abstracts by two authors (DK, NP, SA, RO, JS) led to the retrieval of 191

full papers for screening by two authors (NP, RO, JAS, MU, STC); 69 were included in the

systematic review. (Figure 1). Fifty six studies were case series,(Eischens, Wolf et al. ,

Lnumerables and Fischer-Carlidge , Skibba, Fischer et al. , Wrenn, Sarubbi et al. 2017, Kleris,

Sarubbi et al. 2018, Kyi, Heke et al. 2018, Parker, Choo et al. 2018, Smibert, Douglas et al.

2018, Torney and Tiberg 2018, Wong, Timberlake et al. 2018, Jones, Avramovski et al. 2019,

Patel, Saccone et al. 2019, Rahbani 2019, Blackwell and Khan 2020, Lecerf, Chaparro et al.

2020, Lo, Lacaria et al. 2020, Rahbani and Monroe-Duprey 2020, Phung, Vo et al.

2021)(Harper and Sanchez , Leis, Palmay et al. , Adkinson, Thompson et al. 1971, Harris,

Sauberman et al. 1999, Wall, Peters et al. 2004, Rimawi, Cook et al. 2013, Rimawi and Mazer

2014, Murphy, Scanlan et al. 2015, Heil, Bork et al. 2016, Sigona, Steele et al. 2016, Chen,

Tarver et al. 2017, Gugkaeva, Crago et al. 2017, Jones and Bland 2017, Marwood,

Aguirrebarrena et al. 2017, Trubiano, Smibert et al. 2018, Blumenthal, Li et al. 2019,

Devchand, Kirkpatrick et al. 2019, du Plessis, Walls et al. 2019, Englert and Weeks 2019,

Foolad, Berlin et al. 2019, Savic, Gurr et al. 2019, Taremi, Artau et al. 2019, Allen, Gillespie et

al. 2020, Griffith, Justo et al. 2020, Harmon, Richardson et al. 2020, Lin, Nagtegaal et al.

2020, Livirya, Pithie et al. 2020, Maguire, Hayes et al. 2020, Stone, Stollings et al. 2020,

Bauer, MacBrayne et al. 2021, Ham, Sukerman et al. 2021, Louden, Hansen et al. 2021,

Mitchell, Ness et al. 2021, Morjaria, Inumerables et al. 2021, Sneddon, Cooper et al. 2021,

Song, Nelson et al. 2021, Steenvoorden, Bjoernestad et al. 2021, Torney and Tiberg 2021)

ten were quasi-experimental studies, (Ravindran, Beshir et al. 2017, Nguyen, Sahbani et al. 2019, Stein, MacBrayne et al. 2020)(Blumenthal, Shenoy et al. 2015, Shannon and Krop 2016, Trubiano, Thursky et al. 2017, Trubiano, Thursky et al. 2017, Chen, Tarver et al. 2018, Jones, Avramovski et al. 2019, Jones, Avramovski et al. 2019, Sacco, Cochran et al. 2019, Sacco, Cochran et al. 2019, Gaudreau, Bourque et al. 2021) two were cohort studies,(Chua, Vogrin et al. 2020, Trubiano, Vogrin et al. 2022) and one RCT.(Vyles, Chiu et al. 2020)

Methodological quality

Of fifty-six case series studies, six, 19, and 31 had a high, moderate and low risk of bias, respectively. Risk of bias assessments are shown in appendix 5.

Characteristics of included studies

The 69 included studies reported on the successful PADL of 5019 patients (adults n= 4314;(Eischens, Wolf et al. , Harper and Sanchez , Leis, Palmay et al. , Lnumerables and Fischer-Cartlidge , Skibba, Fischer et al. , Adkinson, Thompson et al. 1971, Harris, Sauberman et al. 1999, Wall, Peters et al. 2004, Rimawi and Mazer 2014, Blumenthal, Shenoy et al. 2015, Heil, Bork et al. 2016, Shannon and Krop 2016, Sigona, Steele et al. 2016, Chen, Tarver et al. 2017, Gugkaeva, Crago et al. 2017, Jones and Bland 2017, Marwood, Aguirrebarrena et al. 2017, Trubiano, Thursky et al. 2017, Wrenn, Sarubbi et al. 2017, Chen, Tarver et al. 2018, Kyi, Heke et al. 2018, Parker, Choo et al. 2018, Smibert, Douglas et al. 2018, Torney and Tiberg 2018, Trubiano, Smibert et al. 2018, Blumenthal, Li et al. 2019, Devchand, Kirkpatrick et al. 2019, du Plessis, Walls et al. 2019, Englert and Weeks 2019, Foolad, Berlin et al. 2019, Jones, Avramovski et al. 2019, Jones, Gamble et al. 2019, Nguyen, Sahbani et al. 2019, Patel, Saccone et al. 2019, Sacco, Cochran et al. 2019, Savic, Gurr et al. 2019, Taremi, Artau et al.

2019, Blackwell and Khan 2020, Chua, Vogrin et al. 2020, Griffith, Justo et al. 2020, Harmon, Richardson et al. 2020, Lin, Nagtegaal et al. 2020, Livirya, Pithie et al. 2020, Lo, Lacaria et al. 2020, Maguire, Hayes et al. 2020, Stone, Stollings et al. 2020, Gaudreau, Bourque et al. 2021, Ham, Sukerman et al. 2021, Mitchell, Ness et al. 2021, Morjaria, Inumerables et al. 2021, Phung, Vo et al. 2021, Sneddon, Cooper et al. 2021, Song, Nelson et al. 2021, Steenvoorden, Bjoernestad et al. 2021, Torney and Tiberg 2021, Trubiano, Vogrin et al. 2022) children n= 461;(Murphy, Scanlan et al. 2015, Wong, Timberlake et al. 2018, Allen, Gillespie et al. 2020, Lecerf, Chaparro et al. 2020, Rahbani and Monroe-Duprey 2020, Stein, MacBrayne et al. 2020, Vyles, Chiu et al. 2020, Bauer, MacBrayne et al. 2021, Louden, Hansen et al. 2021) unreported n=244.)(Ravindran, Beshir et al. 2017, Kleris, Sarubbi et al. 2018, Rahbani 2019) Studies were from the USA (n=48)(Eischens, Wolf et al. , Harper and Sanchez , Lnumerables and Fischer-Carlidge , Skibba, Fischer et al. , Adkinson, Thompson et al. 1971, Harris, Sauberman et al. 1999, Wall, Peters et al. 2004, Rimawi, Cook et al. 2013, Rimawi and Mazer 2014, Blumenthal, Shenoy et al. 2015, Heil, Bork et al. 2016, Shannon and Krop 2016, Sigona, Steele et al. 2016, Chen, Tarver et al. 2017, Gugkaeva, Crago et al. 2017, Jones and Bland 2017, Ravindran, Beshir et al. 2017, Wrenn, Sarubbi et al. 2017, Chen, Tarver et al. 2018, Kleris, Sarubbi et al. 2018, Parker, Choo et al. 2018, Torney and Tiberg 2018, Blumenthal, Li et al. 2019, Englert and Weeks 2019, Foolad, Berlin et al. 2019, Jones, Avramovski et al. 2019, Jones, Gamble et al. 2019, Nguyen, Sahbani et al. 2019, Patel, Saccone et al. 2019, Rahbani 2019, Sacco, Cochran et al. 2019, Taremi, Artau et al. 2019, Blackwell and Khan 2020, Griffith, Justo et al. 2020, Harmon, Richardson et al. 2020, Lecerf, Chaparro et al. 2020, Maguire, Hayes et al. 2020, Rahbani and Monroe-Duprey 2020, Stein, MacBrayne et al. 2020, Stone, Stollings et al. 2020, Vyles, Chiu et al. 2020, Bauer, MacBrayne et al. 2021, Ham, Sukerman et al. 2021, Louden, Hansen et al. 2021, Mitchell,

Ness et al. 2021, Morjaria, Inumerables et al. 2021, Song, Nelson et al. 2021, Torney and Tiberg 2021) Australia (n=9),(Marwood, Aguirrebarrena et al. 2017, Trubiano, Thursky et al. 2017, Kyi, Heke et al. 2018, Smibert, Douglas et al. 2018, Trubiano, Smibert et al. 2018, Devchand, Kirkpatrick et al. 2019, Chua, Vogrin et al. 2020, Phung, Vo et al. 2021, Trubiano, Vogrin et al. 2022) Canada (n=4),(Leis, Palmay et al. , Wong, Timberlake et al. 2018, Lo, Lacaria et al. 2020, Gaudreau, Bourque et al. 2021) Ireland (n=2),(Murphy, Scanlan et al. 2015, Allen, Gillespie et al. 2020) New Zealand (n=2),(du Plessis, Walls et al. 2019, Livirya, Pithie et al. 2020) the UK (n=2),(Savic, Gurr et al. 2019, Sneddon, Cooper et al. 2021) The Netherlands (n=1)(Lin, Nagtegaal et al. 2020) and Norway (n=1).(Savic, Gurr et al. 2019) Most were inpatient studies (n=56; 81.2%),(Harper and Sanchez , Leis, Palmay et al. , Skibba, Fischer et al. , Adkinson, Thompson et al. 1971, Harris, Sauberman et al. 1999, Wall, Peters et al. 2004, Rimawi, Cook et al. 2013, Rimawi and Mazer 2014, Blumenthal, Shenoy et al. 2015, Heil, Bork et al. 2016, Shannon and Krop 2016, Sigona, Steele et al. 2016, Chen, Tarver et al. 2017, Gugkaeva, Crago et al. 2017, Jones and Bland 2017, Ravindran, Beshir et al. 2017, Trubiano, Thursky et al. 2017, Wrenn, Sarubbi et al. 2017, Chen, Tarver et al. 2018, Kleris, Sarubbi et al. 2018, Kyi, Heke et al. 2018, Parker, Choo et al. 2018, Smibert, Douglas et al. 2018, Torney and Tiberg 2018, Wong, Timberlake et al. 2018, Blumenthal, Li et al. 2019, Devchand, Kirkpatrick et al. 2019, du Plessis, Walls et al. 2019, Englert and Weeks 2019, Foolad, Berlin et al. 2019, Jones, Avramovski et al. 2019, Jones, Gamble et al. 2019, Nguyen, Sahbani et al. 2019, Patel, Saccone et al. 2019, Rahbani 2019, Sacco, Cochran et al. 2019, Taremi, Artau et al. 2019, Blackwell and Khan 2020, Chua, Vogrin et al. 2020, Griffith, Justo et al. 2020, Harmon, Richardson et al. 2020, Lecerf, Chaparro et al. 2020, Lin, Nagtegaal et al. 2020, Livirya, Pithie et al. 2020, Stein, MacBrayne et al. 2020, Stone, Stollings et al. 2020, Bauer, MacBrayne et al. 2021, Gaudreau, Bourque et al. 2021, Ham,

Sukerman et al. 2021, Louden, Hansen et al. 2021, Mitchell, Ness et al. 2021, Phung, Vo et al. 2021, Song, Nelson et al. 2021, Steenvoorden, Bjoernestad et al. 2021, Torney and Tiberg 2021, Trubiano, Vogrin et al. 2022) four in the ED only,(Eischens, Wolf et al. , Marwood, Aguirrebarrena et al. 2017, Maguire, Hayes et al. 2020, Vyles, Chiu et al. 2020) four in the outpatient setting(Allen, Gillespie et al. 2020, Lo, Lacaria et al. 2020, Rahbani and Monroe-Duprey 2020, Morjaria, Inumerables et al. 2021) three conducted in both the inpatient and the outpatient setting(Lnumerables and Fischer-Cartlidge , Murphy, Scanlan et al. 2015, Trubiano, Smibert et al. 2018) one inpatient and peri-op(Sneddon, Cooper et al. 2021) and one peri-op only.(Savic, Gurr et al. 2019) The clinical settings included general / internal medicine (n=23),(Leis, Palmay et al. , Adkinson, Thompson et al. 1971, Rimawi, Cook et al. 2013, Blumenthal, Shenoy et al. 2015, Heil, Bork et al. 2016, Chen, Tarver et al. 2017, Chen, Tarver et al. 2018, Kyi, Heke et al. 2018, Parker, Choo et al. 2018, Blumenthal, Li et al. 2019, Englert and Weeks 2019, Nguyen, Sahbani et al. 2019, Sacco, Cochran et al. 2019, Chua, Vogrin et al. 2020, Harmon, Richardson et al. 2020, Livirya, Pithie et al. 2020, Louden, Hansen et al. 2021, Mitchell, Ness et al. 2021, Sneddon, Cooper et al. 2021, Song, Nelson et al. 2021, Steenvoorden, Bjoernestad et al. 2021, Torney and Tiberg 2021, Trubiano, Vogrin et al. 2022) intensive care (n=12),(Leis, Palmay et al. , Rimawi, Cook et al. 2013, Rimawi and Mazer 2014, Heil, Bork et al. 2016, Chen, Tarver et al. 2018, Blumenthal, Li et al. 2019, Jones, Avramovski et al. 2019, Stone, Stollings et al. 2020, Louden, Hansen et al. 2021, Phung, Vo et al. 2021, Torney and Tiberg 2021, Trubiano, Vogrin et al. 2022) surgery / general surgery (n=10),(Rimawi, Cook et al. 2013, Blumenthal, Shenoy et al. 2015, Heil, Bork et al. 2016, Chen, Tarver et al. 2017, Chen, Tarver et al. 2018, Blumenthal, Li et al. 2019, Jones, Avramovski et al. 2019, Chua, Vogrin et al. 2020, Song, Nelson et al. 2021, Trubiano, Vogrin et al. 2022) oncology (n=11),(Blumenthal, Shenoy et al. 2015, Trubiano, Thursky et al.

2017, Smibert, Douglas et al. 2018, Trubiano, Smibert et al. 2018, Blumenthal, Li et al. 2019, Foolad, Berlin et al. 2019, Jones, Avramovski et al. 2019, Taremi, Artau et al. 2019, Chua, Vogrin et al. 2020, Morjaria, Inumerables et al. 2021, Trubiano, Vogrin et al. 2022) hematology (n=9),(Inumerables and Fischer-Carlidge , Trubiano, Thursky et al. 2017, Smibert, Douglas et al. 2018, Trubiano, Smibert et al. 2018, Foolad, Berlin et al. 2019, Taremi, Artau et al. 2019, Lo, Lacaria et al. 2020, Morjaria, Inumerables et al. 2021, Trubiano, Vogrin et al. 2022) Emergency Department (n=8),(Eischens, Wolf et al. , Rimawi, Cook et al. 2013, Murphy, Scanlan et al. 2015, Marwood, Aguirrebarrena et al. 2017, Blumenthal, Li et al. 2019, Jones, Avramovski et al. 2019, Maguire, Hayes et al. 2020, Vyles, Chiu et al. 2020) paediatrics (n=6),(Wong, Timberlake et al. 2018, Blumenthal, Li et al. 2019, Allen, Gillespie et al. 2020, Lecerf, Chaparro et al. 2020, Stein, MacBrayne et al. 2020, Bauer, MacBrayne et al. 2021) obstetrics & gynaecology (n=5),(Rimawi, Cook et al. 2013, Chen, Tarver et al. 2017, Blumenthal, Li et al. 2019, Jones, Avramovski et al. 2019, Song, Nelson et al. 2021) peri-operative (n=4),(Harris, Sauberman et al. 1999, Savic, Gurr et al. 2019, Rahbani and Monroe-Duprey 2020, Sneddon, Cooper et al. 2021) transplant services (n=3),(Inumerables and Fischer-Carlidge , Trubiano, Thursky et al. 2017, Lo, Lacaria et al. 2020) infectious diseases (n=4),(Trubiano, Thursky et al. 2017, Torney and Tiberg 2018, Jones, Gamble et al. 2019, Sneddon, Cooper et al. 2021) cardiology (n=2),(Blumenthal, Shenoy et al. 2015, Blumenthal, Li et al. 2019) urology (n=1),(Blumenthal, Shenoy et al. 2015) oral maxillofacial surgery (n=1),(Blumenthal, Shenoy et al. 2015) neurology (n=1).(Blumenthal, Li et al. 2019) Most studies attempted to de-label those patients with a low allergy risk history only (n=26),(Blumenthal, Shenoy et al. 2015, Sigona, Steele et al. 2016, Kyi, Heke et al. 2018, Smibert, Douglas et al. 2018, Trubiano, Smibert et al. 2018, Blumenthal, Li et al. 2019, Devchand, Kirkpatrick et al. 2019, du Plessis, Walls et al. 2019,



Nguyen, Sahbani et al. 2019, Sacco, Cochran et al. 2019, Savic, Gurr et al. 2019, Allen, Gillespie et al. 2020, Chua, Vogrin et al. 2020, Lecerf, Chaparro et al. 2020, Lin, Nagtegaal et al. 2020, Livirya, Pithie et al. 2020, Maguire, Hayes et al. 2020, Stein, MacBrayne et al. 2020, Bauer, MacBrayne et al. 2021, Louden, Hansen et al. 2021, Mitchell, Ness et al. 2021, Phung, Vo et al. 2021, Sneddon, Cooper et al. 2021, Song, Nelson et al. 2021, Steenvoorden, Bjoernestad et al. 2021, Trubiano, Vogrin et al. 2022) moderate risk allergy history only (n=21),(Harper and Sanchez , Leis, Palmay et al. , Harris, Sauberman et al. 1999, Wall, Peters et al. 2004, Rimawi, Cook et al. 2013, Rimawi and Mazer 2014, Heil, Bork et al. 2016, Shannon and Krop 2016, Chen, Tarver et al. 2017, Gugkaeva, Crago et al. 2017, Jones and Bland 2017, Marwood, Aguirrebarrena et al. 2017, Torney and Tiberg 2018, Englert and Weeks 2019, Foolad, Berlin et al. 2019, Jones, Avramovski et al. 2019, Jones, Gamble et al. 2019, Taremi, Artau et al. 2019, Harmon, Richardson et al. 2020, Morjaria, Inumerables et al. 2021, Torney and Tiberg 2021) two studies included low and moderated risk histories, (Chen, Tarver et al. 2018, Gaudreau, Bourque et al. 2021) two studies included low, moderate, and high-risk allergy histories,(Trubiano, Thursky et al. 2017, Ham, Sukerman et al. 2021) risk category was unclear in 18 studies.(Eischens, Wolf et al. , Lnumerables and Fischer-Carlidge , Skibba, Fischer et al. , Adkinson, Thompson et al. 1971, Murphy, Scanlan et al. 2015, Ravindran, Beshir et al. 2017, Wrenn, Sarubbi et al. 2017, Kleris, Sarubbi et al. 2018, Parker, Choo et al. 2018, Wong, Timberlake et al. 2018, Patel, Saccone et al. 2019, Rahbani 2019, Blackwell and Khan 2020, Griffith, Justo et al. 2020, Lo, Lacaria et al. 2020, Rahbani and Monroe-Duprey 2020, Stone, Stollings et al. 2020, Vyles, Chiu et al. 2020) (appendix 6).

## Review findings

**Primary outcomes:****Proportion of patients successfully de-labelled and the proportion experiencing harm.**

In the studies with complete data on numbers of patients assessed for PADL (n=47), 11,856 patients were assessed for testing, of which 3720 (31.4%) were de-labelled. (Harper and Sanchez , Leis, Palmay et al. , Adkinson, Thompson et al. 1971, Harris, Sauberman et al. 1999, Rimawi, Cook et al. 2013, Rimawi and Mazer 2014, Murphy, Scanlan et al. 2015, Heil, Bork et al. 2016, Shannon and Krop 2016, Sigona, Steele et al. 2016, Chen, Tarver et al. 2017, Marwood, Aguirrebarrena et al. 2017, Wrenn, Sarubbi et al. 2017, Chen, Tarver et al. 2018, Kyi, Heke et al. 2018, Trubiano, Smibert et al. 2018, Blumenthal, Li et al. 2019, Devchand, Kirkpatrick et al. 2019, du Plessis, Walls et al. 2019, Englert and Weeks 2019, Foolad, Berlin et al. 2019, Jones, Avramovski et al. 2019, Jones, Gamble et al. 2019, Nguyen, Sahbani et al. 2019, Patel, Saccone et al. 2019, Savic, Gurr et al. 2019, Taremi, Artau et al. 2019, Allen, Gillespie et al. 2020, Blackwell and Khan 2020, Chua, Vogrin et al. 2020, Griffith, Justo et al. 2020, Harmon, Richardson et al. 2020, Lecerf, Chaparro et al. 2020, Lin, Nagtegaal et al. 2020, Livirya, Pithie et al. 2020, Lo, Lacaria et al. 2020, Stone, Stollings et al. 2020, Vyles, Chiu et al. 2020, Bauer, MacBrayne et al. 2021, Gaudreau, Bourque et al. 2021, Loudon, Hansen et al. 2021, Mitchell, Ness et al. 2021, Phung, Vo et al. 2021, Sneddon, Cooper et al. 2021, Song, Nelson et al. 2021, Steenvoorden, Bjoernestad et al. 2021, Trubiano, Vogrin et al. 2022) In the studies with complete data on the proportion of tested patients' de-labelled (n=60), 5072 were tested, of which 4698 (92.6%) were de-labelled and 76 (1.5%) were harmed; no serious reactions reported (appendix 7).(Harper and Sanchez , Leis, Palmay et al. , Lnumerables and Fischer-Carlidge , Adkinson, Thompson et al. 1971, Egger, Smith et al. 1997, Harris, Sauberman et al. 1999, Wall, Peters et al. 2004, Rimawi,

Cook et al. 2013, Rimawi and Mazer 2014, Murphy, Scanlan et al. 2015, Heil, Bork et al. 2016, Shannon and Krop 2016, Sigona, Steele et al. 2016, Chen, Tarver et al. 2017, Gugkaeva, Crago et al. 2017, Jones and Bland 2017, Marwood, Aguirrebarrena et al. 2017, Trubiano, Thursky et al. 2017, Wrenn, Sarubbi et al. 2017, Chen, Tarver et al. 2018, Kleris, Sarubbi et al. 2018, Kyi, Heke et al. 2018, Parker, Choo et al. 2018, Smibert, Douglas et al. 2018, Torney and Tiberg 2018, Trubiano, Smibert et al. 2018, Blumenthal, Li et al. 2019, Devchand, Kirkpatrick et al. 2019, du Plessis, Walls et al. 2019, Foolad, Berlin et al. 2019, Jones, Avramovski et al. 2019, Jones, Gamble et al. 2019, Savic, Gurr et al. 2019, Taremi, Artau et al. 2019, Allen, Gillespie et al. 2020, Blackwell and Khan 2020, Chua, Vogrin et al. 2020, Griffith, Justo et al. 2020, Harmon, Richardson et al. 2020, Lecerf, Chaparro et al. 2020, Lin, Nagtegaal et al. 2020, Livirya, Pithie et al. 2020, Lo, Lacaria et al. 2020, Maguire, Hayes et al. 2020, Rahbani and Monroe-Duprey 2020, Stein, MacBrayne et al. 2020, Stone, Stollings et al. 2020, Vyles, Chiu et al. 2020, Bauer, MacBrayne et al. 2021, Gaudreau, Bourque et al. 2021, Ham, Sukerman et al. 2021, Louden, Hansen et al. 2021, Mitchell, Ness et al. 2021, Morjaria, Inumerables et al. 2021, Phung, Vo et al. 2021, Sneddon, Cooper et al. 2021, Song, Nelson et al. 2021, Steenvoorden, Bjoernestad et al. 2021, Torney and Tiberg 2021, Trubiano, Vogrin et al. 2022)

### **Healthcare workers**

A range of HCWs were involved in PenA assessment: pharmacists, doctors, nurses, nurse practitioners, physician associates, medical students, and pharmacy students (Appendix 6). Thirty-seven studies (52%) were multidisciplinary (Eischens, Wolf et al. , Harper and Sanchez , Leis, Palmay et al. , Lnumerables and Fischer-Carlidge , Harris, Sauberman et al. 1999, Wall, Peters et al. 2004, Rimawi and Mazer 2014, Murphy, Scanlan et al. 2015, Blumenthal

KG 2016, Shannon and Krop 2016, Jones and Bland 2017, Marwood, Aguirrebarrena et al. 2017, Trubiano, Thursky et al. 2017, Kleris, Sarubbi et al. 2018, Kyi, Heke et al. 2018, Smibert, Douglas et al. 2018, Torney and Tiberg 2018, Trubiano, Smibert et al. 2018, Blumenthal, Li et al. 2019, Devchand, Kirkpatrick et al. 2019, du Plessis, Walls et al. 2019, Foolad, Berlin et al. 2019, Jones, Avramovski et al. 2019, Patel, Saccone et al. 2019, Savic, Gurr et al. 2019, Taremi, Artau et al. 2019, Chua, Vogrin et al. 2020, Lecerf, Chaparro et al. 2020, Maguire, Hayes et al. 2020, Rahbani and Monroe-Duprey 2020, Stone, Stollings et al. 2020, Gaudreau, Bourque et al. 2021, Morjaria, Inumerables et al. 2021, Sneddon, Cooper et al. 2021, Torney and Tiberg 2021, Trubiano, Vogrin et al. 2022) The rest were uni-disciplinary.(Skibba, Fischer et al. , Adkinson, Thompson et al. 1971, Rimawi, Cook et al. 2013, Heil, Bork et al. 2016, Sigona, Steele et al. 2016, Chen, Tarver et al. 2017, Gugkaeva, Crago et al. 2017, Ravindran, Beshir et al. 2017, Wrenn, Sarubbi et al. 2017, Chen, Tarver et al. 2018, Parker, Choo et al. 2018, Wong, Timberlake et al. 2018, Englert and Weeks 2019, Jones, Gamble et al. 2019, Nguyen, Sahbani et al. 2019, Rahbani 2019, Sacco, Cochran et al. 2019, Allen, Gillespie et al. 2020, Blackwell and Khan 2020, Griffith, Justo et al. 2020, Harmon, Richardson et al. 2020, Lin, Nagtegaal et al. 2020, Livirya, Pithie et al. 2020, Lo, Lacaria et al. 2020, Stein, MacBrayne et al. 2020, Vyles, Chiu et al. 2020, Bauer, MacBrayne et al. 2021, Ham, Sukerman et al. 2021, Loudon, Hansen et al. 2021, Mitchell, Ness et al. 2021, Phung, Vo et al. 2021, Song, Nelson et al. 2021, Steenvoorden, Bjoernestad et al. 2021) All multidisciplinary interventions had at least one doctor. Of the uni-disciplinary studies, twenty were delivered by pharmacists (66%),(Skibba, Fischer et al. , Sigona, Steele et al. 2016, Chen, Tarver et al. 2017, Gugkaeva, Crago et al. 2017, Wrenn, Sarubbi et al. 2017, Chen, Tarver et al. 2018, Parker, Choo et al. 2018, Englert and Weeks 2019, Jones, Gamble et al. 2019, Nguyen, Sahbani et al. 2019, Rahbani 2019, Blackwell and Khan 2020,

Griffith, Justo et al. 2020, Harmon, Richardson et al. 2020, Lo, Lacaria et al. 2020, Ham, Sukerman et al. 2021, Loudon, Hansen et al. 2021, Mitchell, Ness et al. 2021, Phung, Vo et al. 2021, Song, Nelson et al. 2021) 11 by doctors (34%), (Adkinson, Thompson et al. 1971, Wood and Wisniewski 1994, Rimawi, Cook et al. 2013, Heil, Bork et al. 2016, Ravindran, Beshir et al. 2017, Allen, Gillespie et al. 2020, Lin, Nagtegaal et al. 2020, Livirya, Pithie et al. 2020, Stein, MacBrayne et al. 2020, Vyles, Chiu et al. 2020, Bauer, MacBrayne et al. 2021, Steenvoorden, Bjoernestad et al. 2021) and one by nurses (3%). (Lecerf, Chaparro et al. 2020)

### **Interventions**

The number of intervention components in each study, grouped by EPOC category, ranged from 1 to 9 (median 5) The most frequently represented EPOC subcategory was 'packages of care' (58/69 studies) followed by 'care pathway' (44/69), and 'educational meetings' (36/69). (Appendix 8)

### **Secondary outcomes:**

#### **Antimicrobial stewardship**

Forty-two studies (61%) reported antibiotic stewardship outcomes (Appendix 6). (Eischens, Wolf et al. , Harper and Sanchez , Leis, Palmay et al. , Skibba, Fischer et al. , Harris, Sauberman et al. 1999, Wall, Peters et al. 2004, Blumenthal, Shenoy et al. 2015, Heil, Bork et al. 2016, Shannon and Krop 2016, Gugkaeva, Crago et al. 2017, Ravindran, Beshir et al. 2017, Trubiano, Thursky et al. 2017, Wrenn, Sarubbi et al. 2017, Chen, Tarver et al. 2018, Kleris, Sarubbi et al. 2018, Parker, Choo et al. 2018, Smibert, Douglas et al. 2018, Torney and Tiberg

2018, Trubiano, Smibert et al. 2018, Devchand, Kirkpatrick et al. 2019, du Plessis, Walls et al. 2019, Englert and Weeks 2019, Foolad, Berlin et al. 2019, Jones, Avramovski et al. 2019, Patel, Saccone et al. 2019, Rahbani 2019, Sacco, Cochran et al. 2019, Taremi, Artau et al. 2019, Chua, Vogrin et al. 2020, Griffith, Justo et al. 2020, Harmon, Richardson et al. 2020, Lin, Nagtegaal et al. 2020, Lo, Lacaria et al. 2020, Rahbani and Monroe-Duprey 2020, Stein, MacBrayne et al. 2020, Stone, Stollings et al. 2020, Ham, Sukerman et al. 2021, Morjaria, Inumerables et al. 2021, Phung, Vo et al. 2021, Torney and Tiberg 2021, Trubiano, Vogrin et al. 2022) Twenty-five (36%)(Eischens, Wolf et al. , Leis, Palmay et al. , Harris, Sauberman et al. 1999, Blumenthal, Shenoy et al. 2015, Jones and Bland 2017, Ravindran, Beshir et al. 2017, Trubiano, Thursky et al. 2017, Chen, Tarver et al. 2018, Kleris, Sarubbi et al. 2018, Torney and Tiberg 2018, Trubiano, Smibert et al. 2018, du Plessis, Walls et al. 2019, Englert and Weeks 2019, Foolad, Berlin et al. 2019, Jones, Avramovski et al. 2019, Sacco, Cochran et al. 2019, Taremi, Artau et al. 2019, Chua, Vogrin et al. 2020, Griffith, Justo et al. 2020, Lo, Lacaria et al. 2020, Ham, Sukerman et al. 2021, Phung, Vo et al. 2021, Steenvoorden, Bjoernestad et al. 2021, Torney and Tiberg 2021, Trubiano, Vogrin et al. 2022) reported increased use of penicillin, of which ten also reported increased cephalosporin or other beta-lactam usage.(Harper and Sanchez , Harris, Sauberman et al. 1999, Blumenthal KG 2016, Jones and Bland 2017, Ravindran, Beshir et al. 2017, du Plessis, Walls et al. 2019, Englert and Weeks 2019, Foolad, Berlin et al. 2019, Sacco, Cochran et al. 2019, Ham, Sukerman et al. 2021, Trubiano, Vogrin et al. 2022) One study reported increased first line antibiotic use.(Eischens, Wolf et al.)Twenty-two studies (33%) report reductions in glycopeptides, quinolones, aztreonam, carbapenems, clindamycin, cephalosporins, macrolides, and aminoglycosides.(Leis, Palmay et al. , Harris, Sauberman et al. 1999, Wall, Peters et al. 2004, Blumenthal KG 2016, Heil, Bork et al. 2016, Jones and Bland 2017,

Trubiano, Thursky et al. 2017, Torney and Tiberg 2018, Trubiano, Smibert et al. 2018, Devchand, Kirkpatrick et al. 2019, Englert and Weeks 2019, Foolad, Berlin et al. 2019, Jones, Avramovski et al. 2019, Rahbani 2019, Sacco, Cochran et al. 2019, Taremi, Artau et al. 2019, Chua, Vogrin et al. 2020, Griffith, Justo et al. 2020, Rahbani and Monroe-Duprey 2020, Ham, Sukerman et al. 2021, Morjaria, Inumerables et al. 2021, Trubiano, Vogrin et al. 2022) Others report reductions in restricted antibiotic use, more narrow-spectrum beta-lactams prescribed or given the preferred regimen,(Harper and Sanchez , Gugkaeva, Crago et al. 2017, Smibert, Douglas et al. 2018, Devchand, Kirkpatrick et al. 2019) reduced course lengths for deep seated infections and no impact on IV antibiotic use.(Shannon and Krop 2016)

### **Healthcare system impact**

Thirteen studies reported antibiotic cost savings. At a patient level, savings were reported to be between 225 USD to 7,800 USD per de-labelled patient.(Rimawi, Cook et al. 2013, Jones and Bland 2017, Parker, Choo et al. 2018, Foolad, Berlin et al. 2019, Jones, Avramovski et al. 2019) Annual hospital drug savings were reported between \$12,400 USD and \$26,000 USD,(Harris, Sauberman et al. 1999, Heil, Bork et al. 2016) cost savings during the study period were reported to be between \$3,831 and \$24, 905,(Harper and Sanchez , Ravindran, Beshir et al. 2017, Morjaria, Inumerables et al. 2021) one study reported savings as \$74.75 per day per de-labelled patient(Harmon, Richardson et al. 2020) and one reported reduced costs without quantification.(Englert and Weeks 2019) One study reported reduced antibiotic costs, another reported antibiotic costs to be 1.6 and 2.5 times greater for inpatient and outpatient penicillin allergic patients respectively (Appendix 6).(du Plessis, Walls et al. 2019, Englert and Weeks 2019)

Nine studies report staff time taken to skin test patients; an hour or less per patient,(Leis, Palmay et al. , Jones, Avramovski et al. 2019) between one and two hours,(Jones and Bland 2017, Marwood, Aguirrebarrena et al. 2017, Chen, Tarver et al. 2018, Lo, Lacaria et al. 2020, Morjaria, Inumerables et al. 2021) between 2 and 2.5 hours(Torney and Tiberg 2021) and one study reported the time requirement as 0.15FTE pharmacist with 30 minutes a week of pharmacy technician time.(Gaudreau, Bourque et al. 2021) The time to de-label on history alone was between 5 and 15 minutes.(Nguyen, Sahbani et al. 2019, Louden, Hansen et al. 2021, Song, Nelson et al. 2021) (appendix 6).

Three report the cost of skin testing to be between 137 and 175 USD(Jones, Avramovski et al. 2019, Harmon, Richardson et al. 2020, Lo, Lacaria et al. 2020) and one reports no increased costs due to absorption by programmatic resources.(Morjaria, Inumerables et al. 2021) The cost of DPT is reported to be 35.18AUD and direct de-label to have no cost implications.(Chua, Vogrin et al. 2020)

Hospital length of stay was reported to be reduced,(Gugkaeva, Crago et al. 2017, Parker, Choo et al. 2018, du Plessis, Walls et al. 2019) increased(Vyles, Chiu et al. 2020) and not affected by PADL.(Leis, Palmay et al. , Shannon and Krop 2016, Sacco, Cochran et al. 2019, Chua, Vogrin et al. 2020) Mortality and readmission rates were unchanged(Harper and Sanchez , Leis, Palmay et al. , Shannon and Krop 2016, Chua, Vogrin et al. 2020, Trubiano, Vogrin et al. 2022) as were adverse drug events.(Leis, Palmay et al. , Shannon and Krop 2016)

## **Meta-analysis**

### **DDL on history alone**



*Assessed for de-label via DDL*

Eleven had a low risk of bias,(Shannon and Krop 2016, Devchand, Kirkpatrick et al. 2019, du Plessis, Walls et al. 2019, Taremi, Artau et al. 2019, Chua, Vogrin et al. 2020, Griffith, Justo et al. 2020, Livirya, Pithie et al. 2020, Bauer, MacBrayne et al. 2021, Gaudreau, Bourque et al. 2021, Louden, Hansen et al. 2021, Mitchell, Ness et al. 2021, Song, Nelson et al. 2021) and six had a moderate risk of bias.(Harper and Sanchez , Murphy, Scanlan et al. 2015, Jones, Avramovski et al. 2019, Nguyen, Sahbani et al. 2019, Lecerf, Chaparro et al. 2020, Lo, Lacaria et al. 2020) Six studies with incomplete data or high risk of bias were excluded.(Wall, Peters et al. 2004, Jones, Gamble et al. 2019, Patel, Saccone et al. 2019, Rahbani 2019, Sacco, Cochran et al. 2019, Ham, Sukerman et al. 2021) In the meta-analysis 4,350 patients were assessed of which 689 (15.8%) were successfully de-labelled. The proportion of assessed patients de-labelled was 14% (95% CI; 9.0-21%), study heterogeneity was high ( $I^2=97%$ ,  $X^2_{17}<0.01$ ) (appendix 9) with evidence of publication bias (Egger's test p-value=0.2087) (appendix 10).

*Appropriate for de-label via history alone*

Twelve had a low risk of bias,(Harper and Sanchez , Devchand, Kirkpatrick et al. 2019, du Plessis, Walls et al. 2019, Taremi, Artau et al. 2019, Chua, Vogrin et al. 2020, Griffith, Justo et al. 2020, Livirya, Pithie et al. 2020, Bauer, MacBrayne et al. 2021, Gaudreau, Bourque et al. 2021, Louden, Hansen et al. 2021, Mitchell, Ness et al. 2021, Song, Nelson et al. 2021) and seven had a moderate risk of bias.(Wall, Peters et al. 2004, Murphy, Scanlan et al. 2015, Jones, Avramovski et al. 2019, Lecerf, Chaparro et al. 2020, Lo, Lacaria et al. 2020, Ham, Sukerman et al. 2021) Five studies with incomplete data or high risk of bias were

excluded.(Jones, Gamble et al. 2019, Nguyen, Sahbani et al. 2019, Patel, Saccone et al. 2019, Rahbani 2019, Sacco, Cochran et al. 2019) Of 713 patients suitable for DDL, 701 (100%; 95% CI 99%-100%) were successfully de-labelled with no reports of harm. Study heterogeneity was high ( $I^2=63%$ ,  $X^2_{18}<0.01$ ) (appendix 9) and risk of publication bias low (Egger's test p-value=0.0001). (Appendix 10).

### **Direct drug provocation testing**

#### *Assessed for DDPT*

Fifteen had a low risk of bias,(Harper and Sanchez , Trubiano, Smibert et al. 2018, Devchand, Kirkpatrick et al. 2019, du Plessis, Walls et al. 2019, Savic, Gurr et al. 2019, Allen, Gillespie et al. 2020, Chua, Vogrin et al. 2020, Lin, Nagtegaal et al. 2020, Livirya, Pithie et al. 2020, Stone, Stollings et al. 2020, Bauer, MacBrayne et al. 2021, Gaudreau, Bourque et al. 2021, Phung, Vo et al. 2021, Sneddon, Cooper et al. 2021, Steenvoorden, Bjoernestad et al. 2021) and four had a moderate risk of bias.(Murphy, Scanlan et al. 2015, Sigona, Steele et al. 2016, Kyi, Heke et al. 2018, Lecerf, Chaparro et al. 2020) Thirteen studies with incomplete data or high risk of bias were excluded.(Blumenthal KG 2016, Trubiano, Thursky et al. 2017, Smibert, Douglas et al. 2018, Wong, Timberlake et al. 2018, Blumenthal, Li et al. 2019, Jones, Gamble et al. 2019, Patel, Saccone et al. 2019, Sacco, Cochran et al. 2019, Maguire, Hayes et al. 2020, Stein, MacBrayne et al. 2020, Vyles, Chiu et al. 2020, Ham, Sukerman et al. 2021, Trubiano, Vogrin et al. 2022) Of 4207 patients assessed, 844 (27%; 95% CI 18-37%) were successfully de-labelled. Study heterogeneity was high ( $I^2=98%$ ,  $X^2_{16}<0.01$ ) (appendix 9) and risk of publication bias high (Egger's test p-value=0.3452). (Appendix 10).

#### *Tested by DDPT*

Sixteen had a low risk of bias,(Harper and Sanchez , Smibert, Douglas et al. 2018, Trubiano, Smibert et al. 2018, Blumenthal, Li et al. 2019, Devchand, Kirkpatrick et al. 2019, du Plessis, Walls et al. 2019, Savic, Gurr et al. 2019, Allen, Gillespie et al. 2020, Chua, Vogrin et al. 2020, Lin, Nagtegaal et al. 2020, Livirya, Pithie et al. 2020, Stone, Stollings et al. 2020, Bauer, MacBrayne et al. 2021, Phung, Vo et al. 2021, Sneddon, Cooper et al. 2021, Steenvoorden, Bjoernestad et al. 2021) and eight had a moderate risk of bias.(Murphy, Scanlan et al. 2015, Sigona, Steele et al. 2016, Kyi, Heke et al. 2018, Lecerf, Chaparro et al. 2020, Maguire, Hayes et al. 2020, Stein, MacBrayne et al. 2020, Ham, Sukerman et al. 2021, Trubiano, Vogrin et al. 2022) Seven studies with incomplete data or high risk of bias were excluded.(Blumenthal KG 2016, Trubiano, Thursky et al. 2017, Wong, Timberlake et al. 2018, Jones, Gamble et al. 2019, Patel, Saccone et al. 2019, Sacco, Cochran et al. 2019, Vyles, Chiu et al. 2020) Of 1336 patients tested 1288 (98%; 95% CI 97-99%) were successfully de-labelled. Study heterogeneity was low ( $I^2=0\%$ ,  $\tau^2_{22}p=0.56$ ) (appendix 9) and risk of publication bias high (Egger's test p-value=0.1574). (Appendix 10).

#### *Harmed by DDPT*

Sixteen had a low risk of bias(Harper and Sanchez , Smibert, Douglas et al. 2018, Trubiano, Smibert et al. 2018, Blumenthal, Li et al. 2019, Devchand, Kirkpatrick et al. 2019, du Plessis, Walls et al. 2019, Savic, Gurr et al. 2019, Allen, Gillespie et al. 2020, Chua, Vogrin et al. 2020, Lin, Nagtegaal et al. 2020, Livirya, Pithie et al. 2020, Stone, Stollings et al. 2020, Bauer, MacBrayne et al. 2021, Phung, Vo et al. 2021, Sneddon, Cooper et al. 2021, Steenvoorden, Bjoernestad et al. 2021) and nine had a moderate risk of bias.(Murphy, Scanlan et al. 2015, Sigona, Steele et al. 2016, Kyi, Heke et al. 2018, Lecerf, Chaparro et al. 2020, Maguire, Hayes et al. 2020, Stein, MacBrayne et al. 2020, Vyles, Chiu et al. 2020, Ham, Sukerman et al. 2021,

Trubiano, Vogrin et al. 2022) Six studies with incomplete data or high risk of bias were excluded.(Blumenthal, Shenoy et al. 2015, Trubiano, Thursky et al. 2017, Wong, Timberlake et al. 2018, Jones, Gamble et al. 2019, Patel, Saccone et al. 2019, Sacco, Cochran et al. 2019) Of 1376 patients tested 48 (2%; 95% CI 1-3%) were harmed. Study heterogeneity was low ( $I^2=0\%$ ,  $X^2_{24}=0.59$ ) (appendix 9) and risk of publication bias high (Egger's test p-value=0.1646). (Appendix 10).

### **Skin testing followed by drug provocation testing (ST/DPT)**

#### *Assessed for de-label via ST/DPT*

Twelve had a low risk of bias,(Harper and Sanchez , Leis, Palmay et al. , Rimawi, Cook et al. 2013, Rimawi and Mazer 2014, Chen, Tarver et al. 2017, Marwood, Aguirrebarrena et al. 2017, Chen, Tarver et al. 2018, Devchand, Kirkpatrick et al. 2019, Foolad, Berlin et al. 2019, Taremi, Artau et al. 2019, Harmon, Richardson et al. 2020, Gaudreau, Bourque et al. 2021) and two had a moderate risk of bias.(Adkinson, Thompson et al. 1971, Lo, Lacaria et al. 2020) Nine studies with incomplete data or high risk of bias were excluded.(Lnumerables and Fischer-Carlidge , Wall, Peters et al. 2004, Gugkaeva, Crago et al. 2017, Ravindran, Beshir et al. 2017, Trubiano, Thursky et al. 2017, Kleris, Sarubbi et al. 2018, Ham, Sukerman et al. 2021, Morjaria, Inumerables et al. 2021, Torney and Tiberg 2021) Of 2890 patients assessed 925 (41%; 95% CI 24-59%) were successfully de-labelled. Study heterogeneity was high ( $I^2=99\%$ ,  $X^2_{13}=1161.19$  ( $p<0.01$ ) (appendix 9) and risk of publication bias high (Egger's test p-value=0.4934). (Appendix 10).

#### *Tested by ST/DPT*

Fourteen had a low risk of bias,(Harper and Sanchez , Leis, Palmay et al. , Rimawi, Cook et al. 2013, Rimawi and Mazer 2014, Chen, Tarver et al. 2017, Marwood, Aguirrebarrena et al. 2017, Chen, Tarver et al. 2018, Devchand, Kirkpatrick et al. 2019, Foolad, Berlin et al. 2019, Taremi, Artau et al. 2019, Harmon, Richardson et al. 2020, Lo, Lacaria et al. 2020, Gaudreau, Bourque et al. 2021, Torney and Tiberg 2021) and five had a moderate risk of bias.(Adkinson, Thompson et al. 1971, Gugkaeva, Crago et al. 2017, Kleris, Sarubbi et al. 2018, Ham, Sukerman et al. 2021, Morjaria, Inumerables et al. 2021) Four studies with incomplete data or high risk of bias were excluded.(Lnumerables and Fischer-Carlidge , Wall, Peters et al. 2004, Ravindran, Beshir et al. 2017, Trubiano, Thursky et al. 2017) Of 1294 patients tested 1177 (95.0%; 95% CI 90%-99%) were successfully de-labelled. Study heterogeneity was high ( $I^2=87%$ ,  $X^2_{18}=138.65$  ( $p<0.01$ )) (appendix 9) and risk of publication bias low (Egger's test  $p$ -value=0.0199). (Appendix 10).

#### *Harmed by ST/DPT*

Thirteen had a low risk of bias,(Harper and Sanchez , Leis, Palmay et al. , Rimawi, Cook et al. 2013, Rimawi and Mazer 2014, Chen, Tarver et al. 2017, Marwood, Aguirrebarrena et al. 2017, Chen, Tarver et al. 2018, Devchand, Kirkpatrick et al. 2019, Foolad, Berlin et al. 2019, Taremi, Artau et al. 2019, Harmon, Richardson et al. 2020, Gaudreau, Bourque et al. 2021, Torney and Tiberg 2021) and eight had a moderate risk of bias.(Lnumerables and Fischer-Carlidge , Adkinson, Thompson et al. 1971, Wall, Peters et al. 2004, Gugkaeva, Crago et al. 2017, Kleris, Sarubbi et al. 2018, Lo, Lacaria et al. 2020, Ham, Sukerman et al. 2021, Morjaria, Inumerables et al. 2021) Four studies with incomplete data or high risk of bias were excluded.(Ravindran, Beshir et al. 2017, Trubiano, Thursky et al. 2017, Jones, Gamble et al. 2019, Blackwell and Khan 2020) Of 1464 patients tested 19 were harmed (0%; 95% CI

0%-1%). Study heterogeneity was low ( $I^2=21\%$ ,  $X^2_{20}=25.31$  ( $p=0.09$ )) (appendix 9) and risk of publication bias was low (Egger's test  $p$ -value=0.0166). (Appendix 10).

Heterogeneity remained unchanged after sensitivity analysis except for the proportion of patients de-labeled on history alone. (Appendix 11)

## Discussion

Rates of PADL varied from 14-41% depending on PenA assessment method. Less intensive methods that targeted the smaller population of lowest risk patients de-labelled a smaller proportion than those employing more formal testing and included higher risk patients.

Once patients were assessed as suitable for de-labelling, rates of PADL were high ( $\geq 95\%$ ), indicating good acceptability of testing and results. PenA assessment by non-allergists was delivered by a diverse workforce to a diverse patient population and demonstrated the significant opportunity to reduce erroneous penA labels in line with global antibiotic stewardship ambitions. (Shenoy, Macy et al. 2019, Committee 2020, Jeimy, Ben-Shoshan et al. 2020, Sneddon, Cooper et al. 2021, Europe 2021

) This review found that penA assessment by non-allergists was safe: of tested patients 1.7% had a subsequent reaction, but none were serious.

PADL increased penicillin use and reduced non-penicillin use, e.g., quinolones and aztreonam, with associated reduced antibiotic spend. HCW time taken to de-label varied depending on the testing method. Local PADL interventions might need to balance the staff resource available with the potential impact on patient care by prioritising patients according to greatest need, or where PADL has the greatest potential for improved patient

care or health system impact.(Macy and Contreras 2014) The potential antibiotic cost savings are likely to offset the HCW and the skin testing costs,(Macy and Contreras 2014) but the HCW costs are often not/poorly described. PADL is delivered by HCWs and their time has an inherent cost that needs adequately describing to enable appropriate health-economic analysis. The wider and longer-term impact of PADL, due not only to reduced drug acquisition costs but also savings in terms of potential reductions in length of stay and mortality are estimated to have been ten times the cost of allergy testing.(Macy and Contreras 2014, Macy and Shu 2017) The longer-term impact of PADL on patient, health systems and AMR requires further study.

Most interventions protocolised PenA assessment with allergists contributing to the development of protocols. The low number of studies reporting direct access to an allergy expert during the day-to-running of PADL provides reassurance of the effectiveness/safety of these protocols without an allergist present. Education was a key theme supporting the appropriate use of the testing protocols.

PADL was commonly delivered by a small team, or an individual HCW, as an outreach service and always in the hospital setting. Less commonly, the responsible medical team de-labeled patients. Individual HCW, or small teams, limits the reach of PADL across a hospital. The advantage of small teams, or individual delivery of PADL, is a greater likelihood of the requisite knowledge and motivation, but delivery of PADL by the wider workforce may enable a broader reach across the hospital. Adequate knowledge, motivation and competing demands may hinder the delivery of PADL by the wider workforce. Quality improvement methodology(Bauer, MacBrayne et al. 2021, Loudon, Hansen et al. 2021) and financial incentives(Bauer, MacBrayne et al. 2021) have been used to motivate staff, but this

adds further expense and time resource to PADL. Whether PADL is safer and more effective as a small team/individual or delivered by the wider workforce needs further study, and the barriers/enablers to the delivery of PADL at scale need exploration. Given the safety of direct DPT in low-risk patients there is potential to extend this to healthcare settings outside of the hospital but this requires further study.

There was high heterogeneity between studies, with several possible explanations. Risk stratification prior to testing was done on both patient factors and allergy history which varied between studies. Route of DPT administration, location of testing and HCW(s) undertaking testing also varied. Others have reported oral challenges to be better tolerated than IV challenges; challenges in the inpatient setting more likely to be tolerated than in the ambulatory setting; tolerance in children reported to be higher than in adults; although tolerance was reported to be similar between those with and without infection.(Harandian, Pham et al. 2016, DesBiens, Scalia et al. 2020) Some studies only assessed using one method and some studies used all three assessment methods introducing further potential for heterogeneity. Optimisation of testing protocols requires further study and harmonisation.

We found low heterogeneity between studies assessing the proportion of tested patients who were successfully de-labelled, and the proportion harmed, by DDPT. There was high heterogeneity between studies looking at PADL in those identified suitable for DDL, but after the sensitivity analysis and removal of one study the recalculated heterogeneity was low. A similar systematic review of the literature, not restricted to non-allergists, reported the successful de-label of 595 (97%) patients using DDPT and comparable to our findings providing external validity to these data.(DesBiens, Scalia et al. 2020) We report harm post DDPT to be 2%, comparable to the expected 0.5-2% ADR rate in patients without a history of



penA but low when compared to other direct DPT studies.(Shenoy, Macy et al. 2019, DesBiens, Scalia et al. 2020) We found low heterogeneity between ST/DPT studies when looking at harm from de-labelling but heterogeneity was high between studies looking at the proportion of tested patients de-labelled by ST/DPT. We found the rate of harm to be low in our study when compared to other studies reporting penicillin tolerability following ST/OC (1% versus 6%) which may be explained by allergists testing higher risk patients or higher rates of false positive skin in some studies, or differing definitions of harm.(DesBiens, Scalia et al. 2020)

### *Limitations*

All the studies are from high income countries (70% from USA), therefore the findings may not be generalisable to LMICs. However, the proportion of tested patients de-labelled and adverse event rates are similar across studies with data from eight countries.

Most studies were case series, with inherent patient selection bias, and the inclusion of conference abstracts limited the review of methodology. Conference abstracts are limited by the extent of reporting and quality.(Scherer and Saldanha 2019) However, the inclusion of abstracts gives a wider and more representative view of the non-allergist de-label activity, particularly important as full paper publication of conference abstracts is reported to be low.(Scherer and Saldanha 2019) The high heterogeneity between studies limits the certainty of our findings.

To reduce publication bias we searched trial registries, unpublished studies, the bibliographies of included studies and asked known experts in the field for missing studies. Despite this, 5 of 8 funnel plots identified high risk of publication bias.

The side effect rate was reported in those de-labeled on history alone. Given the background rate for a penicillin reaction is 0.5-2%,(Shenoy, Macy et al. 2019)we would expect to see some evidence of harm in the 812 patients de-labelled on history alone upon subsequent penicillin re-exposure. It was not clear how many patients went on to receive a penicillin post de-label. The rate of harm in this patient population requires further study.

The statistical power of  $I^2$  test is limited in meta-analyses with <20 studies and / or the average study sample size was <80, with all the meta-analyses in this study below this threshold.(Huedo-Medina, Sánchez-Meca et al. 2006)

## Conclusions

Non-allergists have used several approaches to assess and PADL, all of which appear to be effective and safe. More comprehensive testing capability allowed a greater proportion of assessed patients to be de-labelled. A diverse workforce has delivered PenA assessment services outside of allergy/Immunology services. The consequences of PADL were reported to be increased use of penicillin, and other beta-lactams, with a subsequent reduction in non-beta-lactam antibiotic use and a reduced antibiotic drug spend. PADL is often limited to individual HCWs or small groups of HCWs within a hospital, predominantly delivered as an outreach service, which limits the impact of PADL. Delivery of PADL by the primary healthcare provider and extending PADL to health-care settings outside the hospital, will broaden the impact of PADL. A small number of studies showed provider delivered PADL to be safe and effective but further studies are required on whole of hospital implementation of PADL delivered by primary provider teams. Studies were from high-income countries, data are also needed from low- and middle-income countries.

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## Conflicts of interest

There is no conflict of interest in this project.

Ethics: the study does not require ethical approval because the meta-analysis is based on published research and the original data are anonymous.

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