Sustaining and spreading penicillin allergy de-labelling: a narrative review of the challenges for service delivery and patient safety

Dr Yogini H Jani

Consultant Pharmacist & Health Foundation Improvement Science Fellow
Centre for Medicines Optimisation Research and Education,
UCLH NHS Foundation Trust & UCL School of Pharmacy,
235 Euston Road, London, NW1 2BU, United Kingdom.
Yogini.jani@nhs.net
020 7874 1271

Dr Iestyn Williams

Reader in Health Policy and Management, Health Services Management Centre, University of Birmingham, Birmingham, West Midlands, United Kingdom

Professor Mamidipudi Thirumala Krishna

Consultant Allergist and Immunologist, University Hospitals Birmingham NHS Foundation Trust and Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, West Midlands, United Kingdom

[*Word count, excluding title page, abstract, references, figures and tables]: 2179*

Keywords: Allergy, penicillin, patient safety, improvement science

Sustaining and spreading penicillin allergy de-labelling: a narrative review of the challenges for service delivery and patient safety

ABSTRACT

Many patients report allergies to penicillin, although in over 90% of these the label of penicillin allergy is shown to be incorrect following comprehensive testing. Inappropriate and inaccurate penicillin allergy labelling is a barrier to antimicrobial stewardship and can lead to patient harm.

This review assesses an emergent evidence base and trend favouring de-labelling using ‘direct’ oral penicillin challenges following a stratified risk assessment of the likelihood and existence of true penicillin allergy, to identify and make recommendations for key components for implementation in standard practice. Research to date has focussed on the feasibility and clinical and financial outcomes of these ‘direct’ de-labelling strategies. There is a paucity of studies exploring the views and engagement of patients and health care professionals, and a gap in the evidence for pre-requisites to safely deliver, sustain and spread the implementation of such services across health systems.

INTRODUCTION

Choice of antibiotic treatment depends on the infection and patient factors including their reported or documented allergy status. Penicillins are the first-line antibiotics for many common infections and sepsis.[1,2] Six to ten percent of the general population[3] and 15-20% of hospital inpatients in the UK and USA carry a penicillin allergy (PenA) label, although emergent research shows that 90-95% of these labels are found to be incorrect following comprehensive allergy testing.[2,4-7] Identification and removal of inaccurate and spurious PenA labels is referred to as de-labelling.

Focus on antimicrobial stewardship (AMS) and concerns of inappropriate use of antimicrobials has led to greater interest in the impact of spurious PenA labels on clinical and operational outcomes, and a call for global action.[8,9] Inaccurate PenA labels are a major barrier to AMS and a patient safety concern. [2,4,10] Large cohort studies from United Kingdom (UK) and United States (US) show that PenA labels enhance the risk of serious hospital acquired infections such as Methicillin Resistant Staphylococcus *aureus* (MRSA), Vancomycin Resistant Enterococci and Clostridioides *difficile* infections.[3,10,11] Furthermore, PenA labels are associated with a higher risk of surgical site infections, lengthened hospital stay and greater use of more expensive antibiotics such as carbapenems and 6-fluoroquinolones. [11-13] The excess cost of alternative antibiotics *per se* in PenA patients has been reported at £250-500k *per annum* in a single National Health Service (NHS) Trust in the UK[14] and an estimated at $64m US dollars attributed to longer hospital stay in PenA patients over a 3 year period in Kaiser Permanante Group of hospitals, S. California, USA.[11]

Reports to the National Reporting and Learning System in the UK highlight an association between harm and allergy status, with nearly a third of all medication incident reports involving patients with known documented allergy to one or more medicines.[15] Potential causative and contributory factors include the fact that the term ‘allergy’ is often used interchangeably for ‘intolerance’, the diverse range of non-immunological reactions that may occur and by errors and inadequacies in clinical documentation.[16] Research has highlighted inadequacies in knowledge, skills and training amongst medical students and healthcare professionals in basic drug allergy history taking.[17,18].

We posit that the gap between developing a PenA de-labelling intervention and implementation into routine practice is likely to be significant. To embed, sustain and spread interventions, we need to understand not just whether interventions are effective, but also the prerequisites for their successful adoption and diffusion, taking into account behavioural and contextual factors.[19] Therefore, effective PenA de-labelling strategies require interventions that are sensitive to context. Whilst de-labelling in specialist allergy clinics is established, there is currently little consensus on the ideal components of de-labelling using oral challenges and associated implementation strategies. The aim of this review is to identify and assess current knowledge in relation to key components for oral de-labelling challenges as reported in the literature.

Allergy status in medical practice

Establishing and documenting information about an individual's response to therapeutic agents is a core component of Good Medical Practice and record keeping.[20,21] In particular, documentation of any adverse responses, either due to known extension of the pharmacological action of the drug, or unexpected, unpredictable reactions that may be genetically determined or immunologically mediated, is key to ensuring avoiding inappropriate re-exposure, ensuring patient safety and optimising continuing care. The term 'allergy' is commonly and nebulously used to refer to and record all adverse responses. With the increasing use and interoperability of electronic health records, any 'allergy' status documentation on the patient's record will transfer across different healthcare settings as part of the core medical information, making accuracy essential. In the UK, national guidance has been issued to facilitate diagnosis and management of drug allergy, with recommendations for assessment, documenting and sharing information with other healthcare professionals, providing information and support to patients, and non-specialist management and referral to specialist services.[16] For the final element, the national guidance sets out the subset of patients, including those with PenA labels, who should be referred to specialist allergy services. Similar recommendations for allergy identification, management and documentation have been made in the US and Australia.[22,23]

PenA de-labelling methods

The diagnosis and assessment process for PenA has historically involved a systematic clinical history, review of previous records, skin tests, and a supervised penicillin oral challenge test (if skin tests are negative). Skin tests are labour intensive, time-consuming, and require specialist input.[24,25] Given the burden of PenA and huge unmet demand for allergy services, PenA tests are not routinely available to hospitalised patients.[26,27] Recent studies have suggested that positive skin tests do not always predict outcomes of an oral penicillin challenge, which is considered the gold standard test to exclude an allergy and confirm clinical tolerance.[24,28-30] This has led to trials of 'direct' oral penicillin challenge in 'low risk' patients (those most unlikely to be allergic based on risk assessment and stratification), thus obviating the need for skin tests without compromising safety and creating opportunities for de-labelling without direct specialist input.

'Direct' oral penicillin challenges to de-label have gained favour on the premise that a vast majority (95-99%) of PenA labels are spurious due to inaccurate and incomplete documentation by healthcare professionals or inadequate patient understanding of what constitutes an allergy.[31,32] The first stage of direct PenA de-labelling involves a comprehensive, structured assessment of the clinical history to establish a level of certainty and likelihood of the reported allergy. Clinical algorithms adapted from expert opinion, published studies and guidelines, have been proposed to aid structured risk stratification by non-specialists.[5,9,33] Paper and computer-based stratification tools have been developed and employed at various stages of the patient's journey by clinicians and pharmacists in hospitalised patients and for

preoperative testing.[5,34-37] Application of these tools results in one of three possible outcomes: removal of spurious PenA label; referral to specialist allergy assessment services for those deemed to be 'high risk'; or confirmation of PenA status.

Models and outcomes of direct oral challenge de-labelling

Recent studies of newer approaches of direct PenA de-labelling using structured review and algorithms have primarily focussed on safety and clinical effectiveness (see table 1). Those conducted in hospital settings have involved a multidisciplinary team as a part of AMS programmes;[37,38] and outpatient de-labelling have mainly involved allergy specialist clinics.[39,40] Patient partnership is key to the success of 'direct' Pen-A de-labelling, however some patients do not consent to participate and even when they do, are not comfortable with re-rexposure.[35,41]

Whilst these studies have generated proof of concept in favour of a 'direct' oral penicillin challenge procedure for PenA de-labelling, they were limited due to number of reasons, including relatively small sample size, little or no assessment of views and perspectives of healthcare professionals[42] and patients regarding their confidence in embedding such an approach into routine clinical practice, lack of exploration of reasons for patients' unwillingness to consent to 'direct' oral challenge or re-expose to penicillins and failure to update medical documentation with the outcome of the 'direct' oral challenge. Although most studies have shown 'direct' oral challenges to be safe (no documented anaphylaxis or serious delayed reactions), relatively mild cutaneous reactions after a 'direct' oral challenge[30,40,43] occur, justifying a place for such an intervention in acute care hospitals with an immediate access to management of allergic reactions.[2,44] Caution and concern about potential false negative tests for those patients where the index drug is amoxicillin-clavulanic acid or flucloxacillin has also been raised, unless these antibiotics are used for the confirmatory challenges.[45,46]

Thus, there is a notable knowledge gap in respect of the requirements new service models and interventions place on the patients, health care professionals and organisations to implement and sustain change. Insights from the implementation literature suggests the need for targeted, theoretically-informed interventions to promote change in health care professional behaviour and address organisational impediments to adoption.[47,48] Importantly, PenA de-labelling studies have not yet addressed pre-requisites with respect to clinical governance frameworks, that are likely to vary between health services in different countries.

Challenges of spread and sustainability

With the growing global interest in PenA de-labelling services to promote AMS and proven benefits in terms of clinical outcomes, one of the challenges is in moving from isolated trials of de-labelling to establishing and spreading this as a model of care within and across different care settings. Clearly it is important to involve patients in clinical decisions prior to undertaking PenA de-labelling, and yet there is little in the

published literature to suggest that their perceptions and concerns have been addressed. Understanding and responding to patient perceptions of risk and reward is crucial to enable high uptake of de-labelling programmes. Evidence indicates that proven treatments can take several years to become embedded into clinical practice.[49] Application of improvement and implementation science approaches to focus on core elements of facets that lead to successful sustenance and spread of such interventions may help.[50] A fundamental aspect of these is a better understanding of not just the intervention, but the contextual and infrastructural aspects that leads to successful improvements, with attention to beliefs and behaviour of patients and healthcare professionals.[51]

The evidence to date for 'direct' PenA de-labelling strategies has focussed on aspects of individual practice and pathways, such as risk stratification, importance of information accuracy and flow, inter-professional communication and training. Longer terms outcomes, as well as broader aspects that are key to implementation spread and sustainability, such as wider organisational determinants and incentives, organisational responses to risk, and psychological factors at the patient and physician level, are less well researched.

A way forward

When designing individual-level interventions to change healthcare professional behaviours, four sets of tasks need to be completed: identifying barriers, selecting intervention components, using theory, and engaging end-users.[48] To sustain evidence-based interventions, multiple facilitators, such as adaptation and alignment, and barriers, such as limited funding and limited resources, have been reported.[51] These elements were reflected in our analysis of the evidence for 'direct' Pen-A de-labelling interventions. We recommend that in order to design, develop, sustain and spread safe and efficient de-labelling interventions the following basic elements and pre-requisites (figure 1) should be considered and evaluated.

- Accurate risk stratification: A number of studies[52] have shown this to be feasible and successful as discussed above. National guidelines have been published in some countries to support the collation of relevant details about adverse responses and reactions on a prospective basis, but do not necessarily lead to a confirmed outcome. Combining these details through electronic health records with validated, structured algorithms would enable standardisation of risk stratification.
- Safe clinical environment: Few studies define the optimal setting and set-up (monitoring protocol, rescue medication requirements) of the clinical environment in which 'direct' oral penicillin challenges should be conducted. This information is essential for the sustainability and spread, as well as the development of business models to commission and deliver services.
- Multidisciplinary team: The involvement of a multidisciplinary team in identifying patients and managing treatment as well as updates to medical records is acknowledged in all studies.

- Trained staff: Most of the studies have involved individuals with a special interest or expertise in allergy; details of additional training for non-specialists to deliver de-labelling interventions are rarely reported. With the multidisciplinary and multi-agency nature of healthcare provision across health and social care sectors, training for all relevant stakeholders and professionals needs to be considered.
- Defined governance framework: Few studies have explicitly considered governance frameworks in de-labelling services. This is crucial to all stakeholders involved in such an intervention due to concerns regarding potential harm to patients and downstream medico-legal consequences.
- Counselling and education tools: The high rate of safe de-labelling without the need for skin tests indicates that patient understanding of allergy and the implications of a PenA label is an area that requires further attention. Similarly, exploring and enhancing healthcare professionals' knowledge, understanding and confidence in communicating with patients about allergies and the role of artificial intelligence systems to support risk stratification also requires further study.
- Updating electronic health records and communication with healthcare professional: Accuracy and completeness of documentation of suspected and confirmed allergy status may be a contributory factor in the overinflated reporting of PenA. There is little evidence of the role of intra-operability between health IT systems in the transfer of allergy-related information across different healthcare settings.

Importantly, future antibiotic use and antibiotic associated adverse reactions should be monitored to determine the sustained effectiveness of the overall de-labelling program.

CONCLUSION

Whilst strategies for 'direct' PenA de-labelling are being developed and tested, information on the behavioural insights and contextual requirements for successful implementation is scarce. The elements required for the sustainability and spread of such initiatives have resource and infrastructure implications. Despite health economic projections regarding clinical and cost-effectiveness through reduction in use of high-cost second line antibiotics, improved clinical outcomes and reduced length of stay, longer term safety outcomes and the business model for the commissioning and design of such services has rarely been reported. Similarly, the factors that influence individual patient and healthcare professional behaviours, and involvement of managerial and operational stakeholders in organisations are poorly understood. Future research and implementation strategies should therefore build on the work to date to address these gaps.

Conflicts of interest: none

Funding information: YJ is a Health Foundation Improvement Science Fellow (cohort 4)

REFERENCES

1. *Public Health England (PHE): English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) Report 2018* London: Public Health England (PHE);2018.
2. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and Management of Penicillin Allergy: A Review. *Jama.* 2019;321(2):188-199.
3. West RM, Smith CJ, Pavitt SH, et al. 'Warning: allergic to penicillin': association between penicillin allergy status in 2.3 million NHS general practice electronic health records, antibiotic prescribing and health outcomes. *J Antimicrob Chemother.* 2019;74(7):2075-2082.
4. Krishna MT, Huissoon AP, Li M, et al. Enhancing antibiotic stewardship by tackling "spurious" penicillin allergy. *Clin Exp Allergy.* 2017;47(11):1362-1373.
5. Blumenthal KG, Shenoy ES, Wolfson AR, et al. Addressing Inpatient Beta-Lactam Allergies: A Multihospital Implementation. *J Allergy Clin Immunol Pract.* 2017;5(3):616-625.e617.
6. Macy E, Ngor EW. Safely diagnosing clinically significant penicillin allergy using only penicilloyl-poly-lysine, penicillin, and oral amoxicillin. *J Allergy Clin Immunol Pract.* 2013;1(3):258-263.
7. Mohamed OE, Beck S, Huissoon A, et al. A Retrospective Critical Analysis and Risk Stratification of Penicillin Allergy Delabeling in a UK Specialist Regional Allergy Service. *J Allergy Clin Immunol Pract.* 2019;7(1):251-258.
8. Stone CA, Jr., Trubiano J, Coleman DT, Rukasin CRF, Phillips EJ. The challenge of de-labeling penicillin allergy. *Allergy.* 2019.
9. Blumenthal KG, Peter JG, Trubiano JA, Phillips EJ. Antibiotic allergy. *Lancet.* 2019;393(10167):183-198.
10. Blumenthal KG, Lu N, Zhang Y, Li Y, Walensky RP, Choi HK. Risk of meticillin resistant. *BMJ.* 2018;361:k2400.
11. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: A cohort study. *J Allergy Clin Immunol.* 2014;133(3):790-796.
12. Powell N, West R, Sandoe J. Impact of penicillin allergy records on carbapenem prescribing: an observational retrospective cohort study. *J Hosp Infect.* 2019;101(4):467-470.
13. Blumenthal KG, Parker RA, Shenoy ES, Walensky RP. Improving Clinical Outcomes in Patients With Methicillin-Sensitive Staphylococcus aureus Bacteremia and Reported Penicillin Allergy. *Clin Infect Dis.* 2015;61(5):741-749.
14. Li M, Krishna MT, Razaq S, Pillay D. A real-time prospective evaluation of clinical pharmaco-economic impact of diagnostic label of 'penicillin allergy' in a UK teaching hospital. *J Clin Pathol.* 2014;67(12):1088-1092.
15. Safety in doses. Improving the use of medicines in the NHS. In: National Patient Safety Agency; 2009.
16. *Drug allergy: diagnosis and management. Clinical guideline [CG183].* London: NICE;2014.
17. Blumenthal KG, Shenoy ES, Hurwitz S, Varughese CA, Hooper DC, Banerji A. Effect of a drug allergy educational program and antibiotic prescribing guideline on inpatient clinical providers' antibiotic prescribing knowledge. *J Allergy Clin Immunol Pract.* 2014;2(4):407-413.
18. Reid EF, Krishna MT, Bethune C. Allergy teaching is suboptimal and heterogeneous in the undergraduate medical curriculum in the UK. *J Clin Pathol.* 2019;72(3):221-224.
19. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. *Implement Sci.* 2009;4:50.
20. Core Information Standards. In. London: The Professional Records Standards Body; 2019.
21. Mathioudakis A, Rousalova I, Gagnat AA, Saad N, Hardavella G. How to keep good clinical records. *Breathe (Sheff).* 2016;12(4):369-373.
22. *National safety and quality health service (NSQHS) standards.* Sydney: Australian Commission on Safety and Quality in Health Care;2017.

23. Safe Practices for Drug Allergies — Using CDS and Health IT In: Partnership for Health IT Patient Safety; 2019.
24. Mirakian R, Leech SC, Krishna MT, et al. Management of allergy to penicillins and other beta-lactams. *Clin Exp Allergy.* 2015;45(2):300-327.
25. Richter AG, Wong G, Goddard S, et al. Retrospective case series analysis of penicillin allergy testing in a UK specialist regional allergy clinic. *J Clin Pathol.* 2011;64(11):1014-1018.
26. *Allergy: the unmet need. A blueprint for better patient care. Report of a working party.* London: Royal College of Physicians (RCP);2003.
27. Warner JO, Kaliner MA, Crisci CD, et al. Allergy practice worldwide: a report by the World Allergy Organization Specialty and Training Council. *Int Arch Allergy Immunol.* 2006;139(2):166-174.
28. Banks TA, Tucker M, Macy E. Evaluating Penicillin Allergies Without Skin Testing. *Curr Allergy Asthma Rep.* 2019;19(5):27.
29. Sundquist BK, Bowen BJ, Otabor U, Celestin J, Sorum PC. Proactive penicillin allergy testing in primary care patients labeled as allergic: outcomes and barriers. *Postgrad Med.* 2017;129(8):915-920.
30. Confino-Cohen R, Rosman Y, Meir-Shafrir K, et al. Oral Challenge without Skin Testing Safely Excludes Clinically Significant Delayed-Onset Penicillin Hypersensitivity. *J Allergy Clin Immunol Pract.* 2017;5(3):669-675.
31. Graudins LV, Ly J, Trubiano J, Aung AK. More than skin deep. Ten year follow-up of delayed cutaneous adverse drug reactions (CADR). *Br J Clin Pharmacol.* 2016;82(4):1040-1047.
32. Harig A, Rybarczyk A, Benedetti A, Zimmerman J. Clarification of Drug Allergy Information Using a Standardized Drug Allergy Questionnaire and Interview. *P T.* 2018;43(8):480-504.
33. Blumenthal KG, Wickner PG, Hurwitz S, et al. Tackling inpatient penicillin allergies: Assessing tools for antimicrobial stewardship. *J Allergy Clin Immunol.* 2017;140(1):154-161.e156.
34. Savic LC, Khan DA, Kopac P, et al. Management of a surgical patient with a label of penicillin allergy: narrative review and consensus recommendations. *Br J Anaesth.* 2019;123(1):e82-e94.
35. Savic L, Gurr L, Kaura V, et al. Penicillin allergy de-labelling ahead of elective surgery: feasibility and barriers. *Br J Anaesth.* 2019;123(1):e110-e116.
36. Chen JR, Tarver SA, Alvarez KS, Tran T, Khan DA. A Proactive Approach to Penicillin Allergy Testing in Hospitalized Patients. *J Allergy Clin Immunol Pract.* 2017;5(3):686-693.
37. Devchand M, Kirkpatrick CMJ, Stevenson W, et al. Evaluation of a pharmacist-led penicillin allergy de-labelling ward round: a novel antimicrobial stewardship intervention. *J Antimicrob Chemother.* 2019;74(6):1725-1730.
38. Trubiano JA, Thursky KA, Stewardson AJ, et al. Impact of an Integrated Antibiotic Allergy Testing Program on Antimicrobial Stewardship: A Multicenter Evaluation. *Clin Infect Dis.* 2017;65(1):166-174.
39. Mill C, Primeau MN, Medoff E, et al. Assessing the Diagnostic Properties of a Graded Oral Provocation Challenge for the Diagnosis of Immediate and Nonimmediate Reactions to Amoxicillin in Children. *JAMA Pediatr.* 2016;170(6):e160033.
40. Iammatteo M, Alvarez Arango S, Ferastraoaru D, et al. Safety and Outcomes of Oral Graded Challenges to Amoxicillin without Prior Skin Testing. *J Allergy Clin Immunol Pract.* 2019;7(1):236-243.
41. du Plessis T, Walls G, Jordan A, Holland DJ. Implementation of a pharmacist-led penicillin allergy de-labelling service in a public hospital. *J Antimicrob Chemother.* 2019.
42. Trubiano JA, Beekmann SE, Worth LJ, et al. Improving Antimicrobial Stewardship by Antibiotic Allergy Delabeling: Evaluation of Knowledge, Attitude, and Practices Throughout the Emerging Infections Network. *Open Forum Infect Dis.* 2016;3(3):ofw153.

43. Labrosse R, Paradis L, Lacombe-Barrios J, et al. Efficacy and Safety of 5-Day Challenge for the Evaluation of Nonsevere Amoxicillin Allergy in Children. *J Allergy Clin Immunol Pract.* 2018;6(5):1673-1680.
44. Macy E, Vyles D. Who needs penicillin allergy testing? *Ann Allergy Asthma Immunol.* 2018;121(5):523-529.
45. Meng J, Thursfield D, Lukawska JJ. Allergy test outcomes in patients self-reported as having penicillin allergy: Two-year experience. *Ann Allergy Asthma Immunol.* 2016;117(3):273-279.
46. Confino-Cohen R, Rosman Y, Lachover I, Meir Shafrir K, Goldberg A. The Importance of Amoxicillin and Amoxicillin-Clavulanate Determinants in the Diagnosis of Immediate Allergic Reactions to β-Lactams. *Int Arch Allergy Immunol.* 2016;170(1):62-66.
47. Atkins L, Francis J, Islam R, et al. A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. *Implement Sci.* 2017;12(1):77.
48. Colquhoun HL, Squires JE, Kolehmainen N, Fraser C, Grimshaw JM. Methods for designing interventions to change healthcare professionals' behaviour: a systematic review. *Implement Sci.* 2017;12(1):30.
49. Morris ZS, Wooding S, Grant J. The answer is 17 years, what is the question: understanding time lags in translational research. *J R Soc Med.* 2011;104(12):510-520.
50. Wensing M, Grol R. Knowledge translation in health: how implementation science could contribute more. *BMC Med.* 2019;17(1):88.
51. Hailemariam M, Bustos T, Montgomery B, Barajas R, Evans LB, Drahota A. Evidence-based intervention sustainability strategies: a systematic review. *Implement Sci.* 2019;14(1):57.
52. Krishna MT, Misbah SA. Is direct oral amoxicillin challenge a viable approach for 'low-risk' patients labelled with penicillin allergy? *J Antimicrob Chemother.* 2019.
53. Kuruvilla M, Shih J, Patel K, Scanlon N. Direct oral amoxicillin challenge without preliminary skin testing in adult patients with allergy and at low risk with reported penicillin allergy. *Allergy Asthma Proc.* 2019;40(1):57-61.
54. Trubiano JA, Smibert O, Douglas A, et al. The Safety and Efficacy of an Oral Penicillin Challenge Program in Cancer Patients: A Multicenter Pilot Study. *Open Forum Infect Dis.* 2018;5(12):ofy306.
55. Arnold A, Sommerfield A, Ramgolam A, et al. The role of skin testing and extended antibiotic courses in assessment of children with penicillin allergy: An Australian experience. *J Paediatr Child Health.* 2019;55(4):428-432.
56. Lachover-Roth I, Sharon S, Rosman Y, Meir-Shafrir K, Confino-Cohen R. Long-Term Follow-Up After Penicillin Allergy Delabeling in Ambulatory Patients. *J Allergy Clin Immunol Pract.* 2019;7(1):231-235.e231.
57. Moussa Y, Shuster J, Matte G, et al. De-labeling of β-lactam allergy reduces intraoperative time and optimizes choice in antibiotic prophylaxis. *Surgery.* 2018.
58. Vyles D, Chiu A, Routes J, et al. Antibiotic Use After Removal of Penicillin Allergy Label. *Pediatrics.* 2018;141(5).
59. Vyles D, Adams J, Chiu A, Simpson P, Nimmer M, Brousseau DC. Allergy Testing in Children With Low-Risk Penicillin Allergy Symptoms. *Pediatrics.* 2017;140(2).
60. Vyles D, Chiu A, Simpson P, Nimmer M, Adams J, Brousseau DC. Parent-Reported Penicillin Allergy Symptoms in the Pediatric Emergency Department. *Acad Pediatr.* 2017;17(3):251-255.

Table 1: Overview of oral penicillin challenge studies in the last five years (2014-2019)

Author & year	Patients	Setting and country	Intervention	Context details	Consent	Patient perceptions	Staff perceptions	Safety follow up outcomes
Savic et al 2019[34]	Adults 119/219 patients stratified as low risk	Pre-surgical assessment UK	Risk-stratified screening questionnaire Direct oral challenge – 10%, 50% and 100% (500mg) amoxicillin and 3 day course at home Hospital record updated; letter to general practitioner 5 – 7 day post clinic follow up for delayed symptoms 3 month follow up to check GP record	Dedicated de-labelling clinic Facility to test for alternatives Full resuscitation equipment and Personnel available 20 minutes between increments 1 hour observation afterwards	163/219 agreed to testing Of which 98/119 were classified low risk	For the 55 successfully delabelled patients - 35/43 no anxiety on day - 30/43 not happy with removal without testing 56 patients declined testing - 25 never take whatever the result - 11 not happy to take part in research - 8 not time - 12 other/ unknown	Not assessed	56 underwent challenge 1 urticaria after second dose 4 mild non-allergic symptoms during 3 day course but completed course 2 patients penicillin avoided for surgical prophylaxis despite negative challenge 47/55 GP record correct;

Author & year	Patients	Setting and country	Intervention	Context details	Consent	Patient perceptions	Staff perceptions	Safety follow up outcomes
								3/55 retained allergy label.
du Plessis et al 2019[41]	Adults 250 eligible hospitalised patients	Tertiary hospital New Zealand	Electronic and manual review of allergy status by pharmacists Interview undertaken by pharmacist with outcomes of - Delabel without challenge - Oral challenge* under supervision - Referral to immunology clinic *placebo, placebo, 5 mg, 50 mg, 500 mg (all suspension, in yoghurt)	Exact location not specified Supervision by the primary treating team Pharmacist trained in preparation and administration of oral challenges at a local immunology clinic Doses given 30 minutes apart and for 24 hours afterwards, unless a full course was indicated	3 declined 250 included	At discharge 119/199 delabelled patients happy to take again 57 only if there was no option 23 still not comfortable At 1 year 159/186 agreeable to taking	Not assessed	199/250 delabelled: 160 with no challenge; 31 after oral challenge; 8 referred to clinic 51 label confirmed: 24 with no challenge 3 with challenge (rash with or without itchiness at 27, 29 and 42 hours post dose) 24 referred 23 lost to follow up (13 delabeled; 10

Author & year	Patients	Setting and country	Intervention	Context details	Consent	Patient perceptions	Staff perceptions	Safety follow up outcomes
			Patient education irrespective of outcome; information about applying for Medic-Alert bracelet Letters to patients and primary care practitioners with outcome of interview and any intervention Electronic medical records updated after interventions 1 month and 1 year telephone interview					confirmed allergy) 3/186 delabelled patients were re-labelled due to delayed reactions after re-exposure

Author & year	Patients	Setting and country	Intervention	Context details	Consent	Patient perceptions	Staff perceptions	Safety follow up outcomes
Kuruvilla et al 2019[53]	Adults 50 patients with penicillin allergy labels out of 355 seen in an allergy clinic	Outpatient allergy clinic United States	Review of electronic medical record to identify patients Algorithm for risk stratification Delabelling without oral challenge if reaction was gastro-intestinal upset or had received penicillin after the original label Direct oral challenge for those with penicillin exposure more than 12 months ago	Allergy clinic Baseline monitoring of vital signs and every 30 minutes for 60 mintues after therapeutic dose.	20/38 who met criteria consented 18/38 declined; 9 due to apprehension about recurrent reactions.	Only assessed in 9 of 18 patients who declined	Not assessed	4 delabelled with no oral challenge 3 patients developed subjective reactions not considered positive challenges: diffuse pruritus, chest tightness and dizziness No reports of delayed reactions

Author & year	Patients	Setting and country	Intervention	Context details	Consent	Patient perceptions	Staff perceptions	Safety follow up outcomes
			and lower risk using single dose of 500mg Electronic medical record updated after intervention.					
Trubiano et al 2018[54]	Adults 98 of 195 inpatients and outpatients with penicillin allergy considered low risk.	Cancer patients Australia	Electronic medical record to identify patients Algorithm for risk stratification Low risk patients given oral challenge: either oral penicillin VK 250 mg or amoxicillin 250 mg with prolonged 5 day challenge (250mg twice a	Infectious diseases and antimicrobial stewardship services and outpatient antimicrobial stewardship led allergy testing service Service provided by allergy nurse and infectious disease physician Observed for 2 hours and followed up for 5 days	2 declined 46 consented 50 did not meet inclusion criteria	Not assessed	Not assessed	All patients delabelled with no adverse drug reactions in the 90 days after oral challenge

Author & year	Patients	Setting and country	Intervention	Context details	Consent	Patient perceptions	Staff perceptions	Safety follow up outcomes
			day) for those with a history of delayed reactions.					
Arnold et al 2019[55]	Paediatrics 176 children assessed for beta lactam allergy	Tertiary paediatric hospital Australia	Retrospective review of standard care of direct oral penicillin challenge only or direct oral penicillin challenge with skin testing (if skin testing negative) depending on preference of person treating Oral penicillin challenge with suspected culprit antibiotic by administering one tenth and then a full dose	Allergy specialist/ immunologists service Observations for 1 hour after challenge	Not known as retrospective study of those who had consented to attend allergy clinic	Not assessed	Not assessed	Oral challenge only - 3 reacted Oral challenge after negative skin testing – 4 reacted 3 of the 7 who reacted experienced anaphylaxis 6/132 children with negative oral penicillin challenge reacted to extended course

Author & year	Patients	Setting and country	Intervention	Context details	Consent	Patient perceptions	Staff perceptions	Safety follow up outcomes
			of the antibiotic 30 min apart if there was no reaction to the first dose 5 day extended course for successful oral penicillin challenge					
Lachover-Roth et al 2019[56]	Adults and paediatrics 741 of 784 ambulatory patients evaluated for penicillin allergy	Outpatient allergy unit Israel	Retrospective review Oral challenge test for 5 days following a skin test. Medical records review to assess antibiotic purchase after allergy evaluation	Allergy and clinical immunology unit	Not known as retrospective study of those who had consented to attend allergy clinic	Yes – 579 patients surveyed 96 would be willing to use penicillin 163 refused to use - lack of conviction of safety - inadequate understanding of results	No, but patient survey indicated that a number of family physicians refused to prescribe	53/741 reacted during oral challenge test 19/344 survey patients reported adverse reactions 366/654 who were delabelled still had a penicillin allergy label on their electronic

Author & year	Patients	Setting and country	Intervention	Context details	Consent	Patient perceptions	Staff perceptions	Safety follow up outcomes
			Phone survey to determine re-exposure after allergy evaluation, reactions and perceptions to re-exposure			- refusal of family physician to prescribe		medical record, with 238 patients having purchased or been prescribed penicillin regardless
Moussa et al 2018[57,58]	Adults 190 of 194 preoperative patients assessed for beta lactam de-labelling	Preoperative patients Canada	3 step process 1) Allergy unit consultation to determine likelihood of allergy 2) Risk assessment 3) Testing with skin testing followed by oral challenge - single dose of 300mg penicillin V	Preoperative staff involved in referral Experienced clinical staff performed clinical evaluations and testing. Tests performed in interventional allergy care unit. Allergist supervised for up to 2 hours after last test dose	All	Not assessed	Not assessed	44 patients delabelled without oral challenge based on skin test results and history 7 confirmed allergic by oral challenge

Author & year	Patients	Setting and country	Intervention	Context details	Consent	Patient perceptions	Staff perceptions	Safety follow up outcomes
			or 500mg amoxicillin for low risk patients - graded challenge of same drugs at 10%, 30% and full dose for high risk patients Patients called 24 hours post testing to report delayed reactions Electronic medical records updated	Basic monitoring for an hour after single dose Intensive supervision for graded challenge: recliner chair, intravenous access and frequent vital sign and pulmonary function monitoring				
Vyles et al 2017[59,60]	Paediatrics 100 of 352 children	Paediatric emergency department	Risk assessment using penicillin	Testing by paediatric emergency medicine or	82/434 classified low risk not interested	81/100 parents surveyed	No assessment of perceptions	100 patients delabelled

Author & year	Patients	Setting and country	Intervention	Context details	Consent	Patient perceptions	Staff perceptions	Safety follow up outcomes
and 2018[58]	with low risk symptoms	United States	allergy questionnaire 3 tier penicillin testing: 1) Skin testing 2) Oral challenge - Single dose of 500mg amoxicillin if negative skin test - Graded dosing if positive skin test Electronic medical record updated Follow up with parents and primary care provider	allergy and/or immunology fellows who were trained in allergy testing by a board-certified allergist		- 90% aware of child being delabelled - 59 would be comfortable to re-expose to penicillin - 19 somewhat comfortable and 3 not comfortable as fearful of repeat reaction	but 98/100 primary care physicians surveyed - 82 informed by patient families of delabelling - 51 still had allergy label in medical record	36 required antibiotics in follow up period, received 13 prescriptions of azithromycin, 26 prescriptions of penicillins and 7 of cephalosporins

Author & year	Patients	Setting and country	Intervention	Context details	Consent	Patient perceptions	Staff perceptions	Safety follow up outcomes
Sundquist et al 2017[29]	Adults and Paediatrics 82 patients with penicillin allergy listing	Allergy and immunology practice United states	Electronic health record identification Review by allergist for exclusions 3 step allergy testing process: 2 skin tests, followed by oral challenge using 250g amoxicillin in those with negative skin tests. Patient counselling including information about adverse drug reactions, that would not	Dedicated clinic Monitored for 60 minutes after oral challenge	12/82 declined 7/82 agreed but did not attend 1/37 who were skin tested opted out of oral challenge	1 week and 6 month follow up 28/31 who were followed up at 6 months would take penicillin/ amoxicillin in the future if prescribed. All 31 thought penicillin allergy testing provided important medical information	7/8 referring physicians completed an online survey Estimated that of 50% of their patients with allergy who were asked to participate, less then 50% agreed. Perceived barriers to recruitment (scored 1-10 where 10 is most important) - Patient did want to take time (9.43)	None tested positive to oral challenge 2 reported delayed non-allergic reactions 3/11 who were subsequently prescribed antibiotics received penicillin/ amino-penicillin antibiotic

Author & year	Patients	Setting and country	Intervention	Context details	Consent	Patient perceptions	Staff perceptions	Safety follow up outcomes
			be considered allergy Letter for patient and primary care physician				- Physician lacked time to discuss testing with patient during the visit (7.86). - Patient not wanting to risk having a reaction (5.43) or taking part in research (5.14) - Physician forgot to discuss (5.43) or did not know patient	

Author & year	Patients	Setting and country	Intervention	Context details	Consent	Patient perceptions	Staff perceptions	Safety follow up outcomes
							had an allergy (4.14)	
Chen et al 2017[36]	Adults 252/1203 patients with a penicillin allergy flag	Multidisciplinary inpatient allergy service in large academic hospital United States	Electronic health record associated algorithms for identifying and prioritising patients Review by pharmacist screening for testing Oral challenge to amoxicillin 500mg orally if skin tests were negative Removal of allergy label and results in notes	Multidisciplinary team; pharmacist led screening with allergist on-call to address queries. Testing materials streamlined An emergency reaction kit (epinephrine and diphenhydramine) carried by pharmacists Referrals through use of electronic algorithm or direct referral Patients monitored for 60	Not reported	Not assessed	Not assessed	252 evaluated of which 5 delabelled during interview as previously tested. 1 patient developed urticaria within an hour of oral challenge 16 relabelled despite successful delabelling documentation, education and counselling

Author & year	Patients	Setting and country	Intervention	Context details	Consent	Patient perceptions	Staff perceptions	Safety follow up outcomes
			Physicians and patients individually informed and counselled about the results and implications for future penicillin use	minutes after challenge				

Figure 1: Proposed pre-requisites of a penicillin allergy oral challenge de-labelling programme