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

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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.\textsuperscript{1,2} Six to ten percent of the general population\textsuperscript{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.\textsuperscript{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.\textsuperscript{8,9} Inaccurate PenA labels are a major barrier to AMS and a patient safety concern.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{16} Research has highlighted inadequacies in knowledge, skills and training amongst medical students and healthcare professionals in basic drug allergy history taking.\textsuperscript{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.\textsuperscript{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. 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. 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.

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. Given the burden of PenA and huge unmet demand for allergy services, PenA tests are not routinely available to hospitalised patients. 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. 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. 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. 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. 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; and outpatient de-labelling have mainly involved allergy specialist clinics. 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-exposure.

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 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 occur, justifying a place for such an intervention in acute care hospitals with an immediate access to management of allergic reactions. 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.

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. 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. 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. 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.

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. To sustain evidence-based interventions, multiple facilitators, such as adaptation and alignment, and barriers, such as limited funding and limited resources, have been reported. 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 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

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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.


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<tr>
<td>Savic et al 2019&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Adults 119/219 patients stratified as low risk</td>
<td>Pre-surgical assessment UK</td>
<td>Risk-stratified screening questionnaire, Direct oral challenge – 10%, 50% and 100% (500mg) amoxicillin and 3 day course at home</td>
<td>Dedicated de-labelling clinic, Facility to test for alternatives, Full resuscitation equipment and Personnel available 20 minutes between increments, 1 hour observation afterwards</td>
<td>163/219 agreed to testing, Of which 98/119 were classified low risk</td>
<td>For the 55 successfully delabelled patients - 35/43 no anxiety on day - 30/43 not happy with removal without testing</td>
<td>Not assessed</td>
<td>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;</td>
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| du Plessis et al 2019 | 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 | Exact location not specified | 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 | Not assessed | 3/55 retained allergy label. 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
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<td>Patient education irrespective of outcome; information about applying for Medic-Alert bracelet</td>
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<td>Letters to patients and primary care practitioners with outcome of interview and any intervention</td>
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<td>Electronic medical records updated after interventions</td>
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<td>1 month and 1 year telephone interview</td>
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<td>3/186 delabelled patients were re-labelled due to delayed reactions after re-exposure</td>
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<td>Kuruvilla et al 2019</td>
<td>Adults 50 patients with penicillin allergy labels out of 355 seen in an allergy clinic</td>
<td>Outpatient allergy clinic United States</td>
<td>Review of electronic medical record to identify patients Algorithm for risk stratification Delabelling without oral challenge if reaction was gastrointestinal upset or had received penicillin after the original label Direct oral challenge for those with penicillin exposure more than 12 months ago</td>
<td>Allergy clinic Baseline monitoring of vital signs and every 30 minutes for 60 minutes after therapeutic dose.</td>
<td>20/38 who met criteria consented 18/38 declined; 9 due to apprehension about recurrent reactions.</td>
<td>Only assessed in 9 of 18 patients who declined</td>
<td>Not assessed</td>
<td>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</td>
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<td>Trubiano et al 2018&lt;sup&gt;54&lt;/sup&gt;</td>
<td>Adults 98 of 195 inpatients and outpatients with penicillin allergy considered low risk.</td>
<td>Cancer patients Australia</td>
<td>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 day).</td>
<td>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.</td>
<td>2 declined 46 consented 50 did not meet inclusion criteria</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>All patients delabelled with no adverse drug reactions in the 90 days after oral challenge</td>
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<td>Arnold et al. 2019</td>
<td>Paediatrics 176 children assessed for beta lactam allergy</td>
<td>Tertiary paediatric hospital Australia</td>
<td>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</td>
<td>Allergy specialist/immunologists service Observations for 1 hour after challenge</td>
<td>Not known as retrospective study of those who had consented to attend allergy clinic</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>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</td>
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<td>Lachover-Roth et al 2019&lt;sup&gt;56&lt;/sup&gt;</td>
<td>Adults and paediatrics</td>
<td>Outpatient allergy unit, Israel</td>
<td>Oral challenge test for 5 days following a skin test. Medical records review to assess antibiotic purchase after allergy evaluation</td>
<td>Allergy and clinical immunology unit</td>
<td>Not known as retrospective study of those who had consented to attend allergy clinic</td>
<td>Yes – 579 patients surveyed 96 would be willing to use penicillin 163 refused to use - lack of conviction of safety - inadequate understanding of results</td>
<td>No, but patient survey indicated that a number of family physicians refused to prescribe</td>
<td>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 records</td>
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<td>Moussa et al 2018&lt;sup&gt;57,58&lt;/sup&gt;</td>
<td>Adults 190 of 194 preoperative patients assessed for beta lactam de-labelling</td>
<td>Preoperative patients Canada</td>
<td>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</td>
<td>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</td>
<td>All</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>44 patients delabelled without oral challenge based on skin test results and history 7 confirmed allergic by oral challenge</td>
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<td>Vyles et al, 2017&lt;sup&gt;59,60&lt;/sup&gt;</td>
<td>Paediatrics 100 of 352 children</td>
<td>Paediatric emergency department</td>
<td>Risk assessment using penicillin</td>
<td>Basic monitoring for an hour after single dose</td>
<td>Intensive supervision for graded challenge: recliner chair, intravenous access and frequent vital sign and pulmonary function monitoring</td>
<td>No assessment of perceptions</td>
<td>100 patients delabelled</td>
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| and 2018⁵⁸   | 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 |
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<tr>
<td>Sundquist et al 2017</td>
<td>Adults and Paediatrics</td>
<td>Allergy and immunology practice United states</td>
<td>Electronic health record identification</td>
<td>Dedicated clinic Monitored for 60 minutes after oral challenge</td>
<td>12/82 declined 7/82 agreed but did not attend 1/37 who were skin tested opted out of oral challenge</td>
<td>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</td>
<td>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)</td>
<td>None tested positive to oral challenge 2 reported delayed non-allergic reactions 3/11 who were subsequently prescribed antibiotics received penicillin/aminopenicillin antibiotic</td>
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<td>Intervention</td>
<td>Context details</td>
<td>Consent</td>
<td>Patient perceptions</td>
<td>Staff perceptions</td>
<td>Safety follow up outcomes</td>
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<td>be considered allergy Letter for patient and primary care physician</td>
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<td>- Physician lacked time to discuss testing with patient during the visit (7.86).</td>
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<td>- Patient not wanting to risk having a reaction (5.43) or taking part in research (5.14)</td>
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<td>- Physician forgot to discuss (5.43) or did not know patient</td>
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<td>Author &amp; year</td>
<td>Patients</td>
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<td>Intervention</td>
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<td>Chen et al 2017&lt;sup&gt;36&lt;/sup&gt;</td>
<td>Adults 252/1203 patients with a penicillin allergy flag</td>
<td>Multidisciplinary inpatient allergy service in large academic hospital United States</td>
<td>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.</td>
<td>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 days.</td>
<td>Not reported</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>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.</td>
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<td>Author &amp; year</td>
<td>Patients</td>
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<td>Physicians and patients individually informed and counselled about the results and implications for future penicillin use</td>
<td>minutes after challenge</td>
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Figure 1: Proposed pre-requisites of a penicillin allergy oral challenge de-labelling programme

- **Patient partnership, education and counselling**
- **Understanding staff and patient behaviour** to enhance uptake of the programme
- **Resource** investment for information technology systems and other infrastructure
- **Communication** of changes to allergy status between healthcare settings
- **Penicillin allergy de-labelling service**
  - **Educate** healthcare professionals in basic aspects of drug allergy history taking and documentation using structured algorithms and tools
  - **Governance**: ‘Fit-for-purpose’ governance systems with prospective assessment of safety and clinical effectiveness
  - **Leadership**: Establish a multidisciplinary team with defined roles, leadership and accountability
  - **Pathways**: Defined patient care pathways for penicillin allergy de-labelling