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Krishna, Mamidipudi Thirumala; Bhogal, Rashmeet; Ng, Bee Yean; Kildonaviciute, Kornelija; Jani, Yogini H.; Williams, Iestyn; Sandoe, Jonathan A.T.; Pollard, Rachel; Jones, Nicola; Dunsmure, Louise; Powell, Neil; Hullur, Chidanand; Balaji, Ariyur; Moriarty, Catherine; Jackson, Beverley; Warner, Amena; Daniels, Ron; West, Robert; Thomas, Caroline; Misbah, Siraj A.

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Infectious Disease Practice

A multicentre observational study to investigate feasibility of a direct oral penicillin challenge in de-labelling 'low risk' patients with penicillin allergy by non-allergy healthcare professionals (SPACE study): Implications for healthcare systems



Mamidipudi Thirumala Krishna ^{a,*}, Rashmeet Bhogal ^b, Bee Yean Ng ^c, Kornelija Kildonaviute ^c, Yogini H. Jani ^d, Iestyn Williams ^e, Jonathan A.T. Sandoe ^f, Rachel Pollard ^g, Nicola Jones ^h, Louise Dunsmure ^c, Neil Powell ⁱ, Chidanand Hullur ^j, Ariyur Balaji ^k, Catherine Moriarty ^l, Beverley Jackson ^l, Amena Warner ^m, Ron Daniels ⁿ, Robert West ^f, Caroline Thomas ^o, Siraj A. Misbah ^{p,1}, Louise Savic ^{o,1}

^a Institute of Immunology and Immunotherapy, University of Birmingham and Department of Allergy and Immunology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

^b Department of Pharmacy, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

^c Department of Pharmacy, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

^d Centre for Medicines Optimisation Research and Education, University College London Hospitals NHS Foundation Trust and UCL School of Pharmacy, London, UK

^e Health Services Management Centre, University of Birmingham, Birmingham, UK

^f Healthcare Associated Infection Group, Leeds Institute of Medical Research, University of Leeds and Leeds Teaching Hospitals NHS Trust, Leeds, UK

^g Department of Anaesthesia, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

^h Department of Infectious Diseases, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

ⁱ Department of Pharmacy, Royal Cornwall Hospitals NHS Trust, Truro, UK

^j Department of Anaesthesia, Birmingham Heartlands Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

^k Acute Medicine Unit, Birmingham Heartlands Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

^l Theatres and Anaesthetics Research Team, St James' University Hospital, Leeds Teaching Hospitals, Leeds, UK

^m Allergy UK, Crayford, UK

ⁿ The UK Sepsis Trust, Walsall, UK

^o Department of Anaesthesia, St James' University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds, UK

^p Department of Clinical Immunology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

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SUMMARY

Objective: The huge burden of inaccurate penicillin allergy labels (PALs) is an important driver of antimicrobial resistance. This is magnified by insufficient allergy specialists and lack of 'point-of-care' tests. We investigated the feasibility of non-allergy healthcare professionals (HCPs) delivering direct oral penicillin challenges (DPCs) for penicillin allergy de-labelling.

Methods: This prospective observational study was conducted in three hospitals in England across three settings (acute medical, pre-surgical and haematology-oncology). Patients with a PAL were screened and stratified as low risk/high risk. Low risk patients (non-immune mediated symptoms, benign rash, tolerated amoxicillin since and family history) underwent a DPC.

Results: N = 2257 PALs were screened, 1054 were eligible; 643 were approached, 373 declined, 270 consented and 259 risk stratified (low risk = 155; high risk = 104). One hundred and twenty-six low risk patients underwent DPC, 122 (96.8%) were de-labelled with no serious allergic reactions.

Conversion rate from screening-to-consent was 12% [3.3% and 17.9% in acute and elective settings respectively; odds ratios for consent were 3.42 (p < 0.001) and 5.53 (p < 0.001) in haematology-oncology and pre-surgical setting respectively. Common reasons for failure to progress in the study included difficulty

* Correspondence to: Institute of Immunology and Immunotherapy, College of Medical and Dental Sciences, Institute of Biomedical Research, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK.

E-mail address: m.t.krishna@bham.ac.uk (M.T. Krishna).

¹ S.A.M. and L.S. are joint senior authors.

in reaching patients, clinical instability/medical reasons, lacking capacity to consent and psychological factors.

Interpretation: DPCs can be delivered by non-allergy HCPs. A high proportion of patients with PALs did not progress in the study pathway. Strategies to deliver DPC at optimal points of the care pathway are needed to enhance uptake. Elective settings offer greater opportunities than acute settings for DPC. The safety and simplicity of DPCs lends itself to adoption by healthcare systems beyond the UK, including in resource-limited settings.

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Introduction

Six and 10% of the population in England and USA respectively carry a penicillin allergy label (PAL),^{1,2} with 15–20% of patients in secondary care declaring an allergy to penicillin.³ However, there is a large body of evidence to suggest that 90–95% of PALs are inaccurate.^{4,5} PALs are linked to enhanced risk of antimicrobial resistance (AMR) and healthcare associated infections such as *Clostridioides difficile*, surgical site infections, lengthened hospital stay and very high estimated healthcare costs.^{6,7} There is no 'point-of-care' test for penicillin allergy, and current standard of care in the UK National Health Service (NHS) involves either prescription of an alternative antibiotic class or assessment by an allergy specialist, and this includes history taking, review of clinical records, skin tests and a challenge test.⁸ Penicillin allergy tests are onerous, time consuming and there is a huge unmet need for allergy specialists globally.⁹

There is emerging evidence and recommendations from the British Society for Allergy and Clinical Immunology (BSACI) regarding a direct oral penicillin challenge (DPC) that circumvents allergy skin testing in patients stratified as 'low risk' based on clinical history and review of clinical records.^{10,11} 'Low risk' patients are highly unlikely to have an immune-mediated reaction following further exposure to a penicillin antibiotic. Previous studies were led by both allergy specialists and non-allergy specialist healthcare professionals (HCPs), and these were largely limited by relatively small sample size and involving a single centre.^{10,12} Whilst the safety of DPC has been established from these studies and recent systematic reviews,^{10,12} data from the UK NHS relating to the proportion of patients with a PAL suitable for consideration of this intervention, reasons for unsuitability, optimal point in patient pathway when DPC may be considered, and appropriateness of the clinical setting are sparse.

In this prospective multi-centre observational study, we tested the feasibility of a non-allergy specialist HCP led DPC in three busy NHS Trusts in England across acute and elective clinical settings. We investigated the clinical pathway for penicillin allergy de-labelling (PADL) from the point of identifying and screening patients with a PAL on clinical records based on standardised criteria, seeking informed consent, risk stratification, administering a DPC to 'low risk' patients followed by a 5-day follow-up to assess for a delayed or type-IV (non-immediate) hypersensitivity reaction (HSR).

Methods

Study design and procedures

This study was conducted between 01 May 2021 and 30 April 2023 across three NHS Trusts in England including University Hospitals Birmingham NHS Foundation Trust (UHB), Leeds Teaching Hospitals NHS Trust and Oxford University Hospitals NHS Foundation Trust. Clinical settings included Acute Medical Unit (AMU)/Infectious Diseases (ID), Pre-surgical and Haematology-Oncology units.

In the UK NHS, patients with an alleged or suspected reaction to any penicillin are labelled with a PAL. A list of inpatients with PALs ≥18 years old was generated from Trust information systems at study sites and patients were screened by research nurses (RNs) and Research Pharmacists (RPs) to determine eligibility as per study criteria (Table 1) for potential inclusion for risk stratification. Patients who were clinically unstable, pregnant, breastfeeding, with concomitant COVID-19 or enrolled in another research were excluded at this stage. Potentially suitable patients were approached by RNs/RPs. All RNs, RPs and study consultants attended pre-study workshops for training and standardisation of study procedures (details in [Supplementary file-1](#)).

Informed consent was sought prior to risk stratification. Risk stratification was conducted as per study criteria (Table 2) by RPs in Birmingham and Oxford and RNs at Leeds. The process included standardised history using a study proforma and review of clinical records in primary and/or secondary care as deemed necessary. Briefly, 'low risk' patients included those reporting a benign rash (not 'hives' or urticaria), thrush and/or other non-immune mediated symptoms only without features of an IgE mediated reaction, those who acquired the label on the basis of a family history or when there was documented evidence of clinical tolerance to amoxicillin or co-amoxiclav since registration of PAL. Patients with severe or brittle asthma, severe COPD, heart failure, history suggestive of a HSR, angioedema or those needing hospitalisation due to the index episode were stratified as 'high risk'. All risk stratification outcomes were reviewed and approved by a senior non-allergy study consultant. Occasionally, specialist allergist input was sought to confirm the outcome of risk stratification.

Table 1
Inclusion and exclusion criteria at screening.

Inclusion criteria:

1. Patients with a current PAL, ≥18 years, with capacity to give informed consent

Exclusion criteria:

1. Clinically unstable patients, i.e., unstable cardio-respiratory status (eg: respiratory failure, cardiac failure, pre-hepatic encephalopathy etc.)
2. History of serious non-immediate systemic hypersensitivity reactions (HSRs) to penicillin
 - a. Documented Steven Johnson syndrome (SJS), toxic epidermal necrolysis (TENS), acute exanthematous generalised pustulosis (AEGS), erythema multiforme, haemolytic anaemia, vasculitis, acute interstitial nephritis
3. Those deemed unsuitable for medical reasons (unlikely to comply with study protocol)
4. Pregnant
5. Breast feeding
6. Concomitant COVID-19 infection
7. Those participating in any other research currently or those who have participated in research involving medicinal product, medical devices and/or other intervention in preceding 6 weeks.
8. Patients currently receiving Omalizumab or those who have received Omalizumab within 6 months prior to proposed DPC
9. Patients currently taking antihistamine and unable to temporarily withdraw from the proposed DPC
10. Patients with significant psychological/psychiatric conditions such as severe anxiety, severe depression, dementia, schizophrenia etc., that is deemed unsuitable for informed consent

Table 2
Risk stratification criteria.

Low risk: Those with one or more of the following:

1. History of nonspecific symptoms *only* (eg: headache, isolated dizziness, gastrointestinal symptoms).
2. Thrush *only*, no other symptoms.
3. Mild 'benign' rash.
4. History of 'childhood rash – no further details available'
5. Pruritus without rash.
6. Gaps in clinical history, but clearly suggestive of a non-life-threatening reaction and did not require hospitalisation.
7. Remote (> 10 years) reactions without features of an IgE mediated reaction.
8. Tolerated treatment with amoxicillin/co-amoxiclav **since** registration of PAL.
9. No history of an 'index episode' but advised to avoid penicillins due to family history.

#benign rash: Check list for a 'benign' rash is summarised as follows:

- I. *Non-blistering, not painful, non-desquamating, non-bruising*
- II. *No associated mouth ulcers/genital ulcers*
- III. *Not systemically unwell due to the reaction*
- IV. *Not hospitalised*

If any of the above criteria were not met or relevant information was not available, patient was stratified as 'high risk'.

High risk: Those with any one or more of the following:

1. Severe, uncontrolled or brittle asthma.
2. Severe COPD.
3. Heart failure or severe impairment in cardiac function.
4. Symptoms suggestive of an IgE mediated reaction or anaphylaxis after administration of penicillins.
5. Blistering, painful, desquamating or bruising rash.
6. Symptoms requiring hospital admission.
7. History of angioedema as a part of index reaction.

DPCs were conducted in a safe clinical environment (on the wards or in an outpatient setting in acute care hospitals) by RNs at Leeds and RPs at Birmingham and Oxford under the supervision of non-allergy study consultant. The clinical settings included immediate access to facilities for management of anaphylaxis, crash trolley, cardio-pulmonary resuscitation and an urgent access to critical care outreach team if needed. All female patients of child-bearing potential underwent a urine pregnancy test prior to DPC. Those on antihistamines withdrew treatment temporarily for 3 days prior to DPC and advised regarding reintroduction post-DPC. Vital parameters were checked at baseline and amoxicillin 500 mg was administered orally as a single dose. Patients were observed for 1 hour and vital parameters were repeated. This was followed by 'opportunistic' or 'therapeutic' de-labelling if there was no evidence for type-I HSR. 'Opportunistic' de-labelling involved a modest dose of 250 mg amoxicillin twice daily for 3 days. This 3-day course was given to patients where the index reaction was unclear with respect to temporal association or when symptoms were delayed or occurred during the treatment course during the index reaction. 'Therapeutic' de-labelling involved a full therapeutic course of appropriate penicillin-based antibiotic as deemed necessary by the patients' clinical team to treat any intercurrent infection after exclusion of type-I HSR. All patients were provided with written instructions ([Supplementary file-2](#)) regarding management of delayed onset allergic reactions alongside contact details of the research team.

For inpatients who commenced 'opportunistic' de-labelling and then developed an intercurrent infection that required a full therapeutic course of amoxicillin or an alternative penicillin-based antibiotic, treatment was switched to an appropriate regimen following discussion between the research team and respective clinical teams.

Patients were contacted to check for delayed onset symptoms up to day 5 post-DPC. The outcome of DPC was communicated directly to patients, their records were updated, and a written communication was forwarded to their general practitioner.

The TIDIER framework,¹³ was used to elicit any site specific contextual descriptions of materials used in the intervention

('What?'), roles involved in delivery of the intervention ('Who?'), modes of delivery ('How?'), location and infrastructure of delivery ('Where?'). The checklist was used to guide group discussions conducted with the key implementing staff in each of the sites.

The study was approved by The London Bridge Ethics Committee (REC Reference 21/PR/0814; IRAS project ID: 293544) on 23 July 2021.

The original total sample size for DPCs was 375. This was revisited and revised in light of low conversion rates [(number consented/number screened) × 100] across the three participating sites during the first 3–4 months of the study. The revised sample size was based on a systematic review¹⁰ involving 1202 patients in 13 studies (inpatient and outpatient 'low risk' with a PAL) that reported ~97% de-labelling with no severe adverse reactions related to DPC. To estimate this rate with a 95% confidence interval (± 3%), a total number of at least 122 DPCs were required across the three participating sites.

Details regarding overarching aims and objectives of the SPACE study as well as workstreams (WSs), original sample size calculation, and other study amendments during the course of the project are summarised in [Supplementary file-3](#). The data presented in this manuscript refers to WS-1 of the SPACE study.

Data were entered on REDCap®. Tables were constructed by collating data from each patient and cross-tabulating patient characteristics against hospital and clinical setting. To aid in the detection of potential associations, continuous variables (age) were compared between the hospital/clinical setting groups using Kruskal-Wallis tests. This was for a guide only and not intended as a definitive test. Similarly, categorical variables (gender) were compared across hospital/clinical settings groups using Pearson chi-squared tests, again for guidance only.

More detailed analysis was provided to compare outcomes, such as de-labelled 'Yes'/'No', with the use of logistic regression. First, the outcome was regressed upon each potential 'risk factor', such as gender, producing an unadjusted odds ratio (OR; by exponentiation of the fitted parameter), and then a multivariable logistic regression used to yield adjusted ORs. Once again, given the observational nature of the data, and since perfect adjustment cannot be guaranteed, the resultant ORs are intended to summarise the observed potential effects and not be interpreted as definitive tests of association.

Patient and Public Involvement and Engagement (PPIE) groups were established at Birmingham and Oxford and regular meeting were held. Study updates including recruitment and data analysis were discussed. Patients and patient representatives from Allergy UK and the UK Sepsis Trust were involved in study design, study protocol including shaping patient facing documents, investigator meetings, data analysis and writeup. This process was in line with Guidance for Reporting Involvement of Patient and Public (GRIPP2) guidance/checklist.¹⁴ All recommendations from our patient partners were considered and implemented during the entire course of the study.

The funder of the study (National Institute for Health and Care Research) had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

A total of 2257 patients (male = 834; female = 1423) with a PAL were identified for screening across the three participating sites. Study flow diagram and details regarding centre and clinical setting-specific data including demographics are summarised in [Figs. 1 and 2](#) and [Tables 3 and 4](#). Following screening, 1054 patients were deemed eligible to proceed through the study pathway. Four hundred and twelve out of the 1054 patients could not be approached due to one or more logistical reasons such as patient being

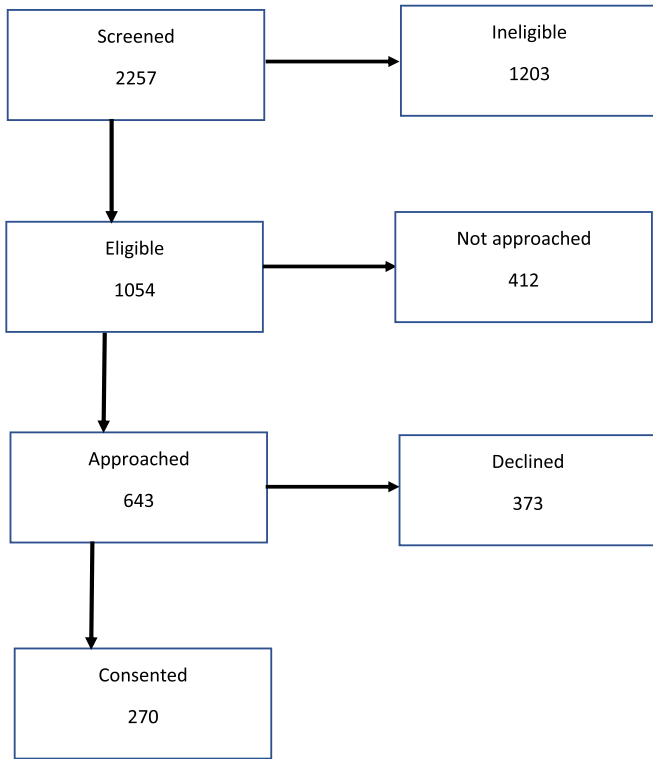


Fig. 1. Flow diagram from screened to consented.

discharged, moved to another location, becoming clinically unstable, not being able to reach the patient by phone or research team not being able to contact the patient. Six hundred and forty-three patients were approached by the research team and 373 declined to

Table 3 Demographics of screened patients.

		Not eligible n = (%)	Eligible n = (%)
Hospital	Birmingham	422 (53.1)	373 (46.9)
	Oxford	239 (50.6)	233 (49.4)
	Leeds	541 (54.6)	449 (45.4)
Clinical setting	AMU/ID	732 (81.3)	168 (18.7)
	Pre-surgical	292 (29.4)	700 (70.6)
	Haem-Oncol	178 (48.8)	187 (51.2)
Age range (years)	< 30	44 (41.9)	61 (58.1)
	30–39	60 (39.7)	91 (60.3)
	40–49	97 (37.9)	159 (62.1)
	50–59	150 (42.9)	200 (57.1)
	60–69	192 (47.4)	213 (52.6)
	70–79	283 (56.3)	220 (43.7)
	≥80	376 (77.2)	111 (22.8)
Gender	Male	432 (51.8)	402 (48.2)
	Female	770 (54.1)	653 (45.9)

participate; 270 (42%) consented (initially 273 were consented and 3 were withdrawn post-consent). Reasons for ineligibility at screening are summarised in Fig. 3.

Out of the total screened sample of 2257, ethnicity data were available for 1972 (87.4%) patients. There were 100 (16%), 64 (7.2%) and 97 (20.1%) patients of non-White ethnicity screened with a PAL at Birmingham, Leeds and Oxford respectively. Overall, the screened study sample included 11.5% patients of non-White ethnicity.

The overall conversion rate (screening-to-consent; Table 5) across all study sites and clinical settings was relatively low at 12% including 13%, 9% and 16% at Birmingham, Leeds and Oxford respectively. The overall conversion rate in an acute setting was very low at 3.3% and relatively higher in Haematology-Oncology (12.9%)

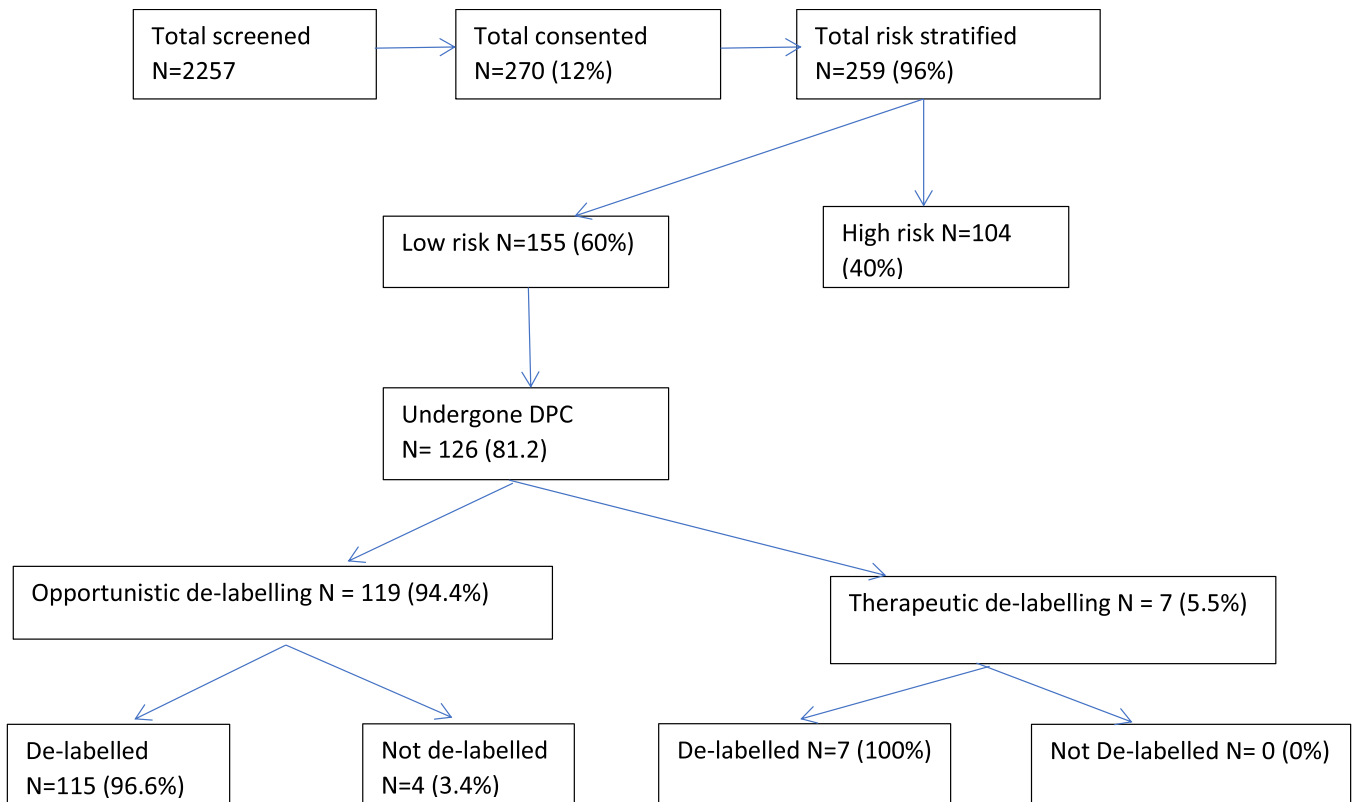


Fig. 2. Study flow diagram.

Table 4
Demographics of consented patients.

	All			AMU/ID unit			Pre-surgical			Haem/Oncol		
	B'ham	Oxford	Leeds	B'ham	Oxford	Leeds	B'ham	Oxford	Leeds	B'ham	Oxford	Leeds
N	102	77	91	10	17	3	61	51	83	31	9	5
Age years (median [IQR])	60.00 [51.50, 69.75]	58.00 [46.00, 68.25]	61.00 [48.00, 73.00]	65.00 [59.50, 75.75]	53.00 [39.00, 69.00]	55.00 [55.00, 67.00]	59.00 [52.00, 70.50]	56.50 [45.75, 64.50]	61.00 [48.00, 73.00]	58.00 [48.00, 68.00]	63.00 [59.00, 70.00]	63.00 [57.00, 69.00]
Gender												
M (%)	41 (40)	32 (42)	43 (47)	4 (40)	7 (41)	1 (33)	19 (31)	20 (39)	38 (46)	18 (58)	5 (56)	4 (80)
F (%)	61 (60)	45 (58)	48 (53)	6 (60)	10 (59)	2 (67)	42 (69)	31 (61)	45 (54)	13 (42)	4 (44)	1 (20)
Ethnicity												
White (%)	62 (61)	61 (79)	80 (88)	7(70)	16 (94)	2 (67)	40 (66)	38 (75)	73 (88)	15 (48)	7 (78)	5 (100)
Non-White (%)	10 (10)	16 (21)	5 (6)	1 (10)	1 (6)	0 (0)	6 (10)	13 (26)	5 (6)	3 (10)	2 (22)	0 (0)
Not recorded (%)	30 (29)	0 (0)	6(7)	2 (20)	0 (0)	1 (33)	15 (25)	0 (0)	5 (6)	13 (42)	0 (0)	0 (0)

and Pre-surgical (19.8%) settings. The combined conversion rate in elective settings across the three sites was 17.9%. Progression in the study pathway (i.e., screening-to-consent) was significantly greater in Oxford (OR-1.68; $p = 0.003$), greater in elective settings including haematology-oncology (OR-3.42; $p < 0.001$) and pre-surgical (OR-5.53; $p < 0.001$). Male patients were significantly more likely (OR-1.38, $p = 0.02$) and those ≥ 80 years (OR-0.23, $p = 0.001$) significantly less likely to progress from screening-to-informed consent.

Two hundred and fifty-nine out of 270 (96%) consented patients were risk stratified. Eleven patients could not undergo stratification for practical reasons such as change in their circumstances or being unreachable despite multiple attempts. One hundred and fifty-five (60%) and 104 (40%) patients were stratified as 'low risk' and 'high risk' respectively. Demographic data on risk stratification is shown in Tables 6 and 7.

One hundred and twenty-six out of 155 (81%) 'low risk' patients agreed to undergo DPC. Four additional DPCs were conducted, as the study team wanted to deliver the intervention to all 'low risk' patients who had consented to DPC. Of the 126 DPCs conducted, 7 (5.5%) were 'therapeutic' and 119 (94.4%) were 'opportunistic' de-labelling. All patients who underwent 'therapeutic' de-labelling were successfully de-labelled, and 115 out of 119 patients (96.6%) who underwent 'opportunistic' de-labelling were successfully de-labelled. Overall, 122 out of 126 patients (97%) were de-labelled. There were no cases of serious type-I or type-IV HSRs. Twenty-seven adverse events occurred, and this included two serious adverse

reactions (SAEs), both deemed 'unlikely to be related to DPC'. These SAEs were subjected to a detailed review by the SPACE team investigators, respective clinical care teams, the study sponsor's research development and innovation department and oversight committee Chairs. Of remaining 25, 3 were deemed mild cutaneous non-immediate HSRs and 22 mild non-immune mediated non-specific. DPC data are summarised in Table 8 and adverse reactions and SAEs are summarised in Table 9 (full details in Supplementary file-4).

Discussion

This is the first multi-centre prospective non-allergy specialist HCP led study from the UK investigating the feasibility of DPCs in secondary care and constitutes the largest cohort of patients with PALs in the context of PADL with over two thousand patients. There were no cases of serious type-I and type-IV HSRs. However, the conversion rate from screening-to-informed consent was very low in an acute clinical setting and significantly higher but modest in elective clinical settings.

Amongst consented patients, 60% were deemed 'low risk' and this is in keeping with previous studies that reported a broad range (40–82%) for 'low risk' category amongst those considered for PADL.^{15–18} We employed amoxicillin for DPC as this is the most commonly prescribed penicillin in the UK, is a representative member of the beta-lactam (penicillin) family and is sufficient to

Reasons for failure to progress from screening (N=1203)

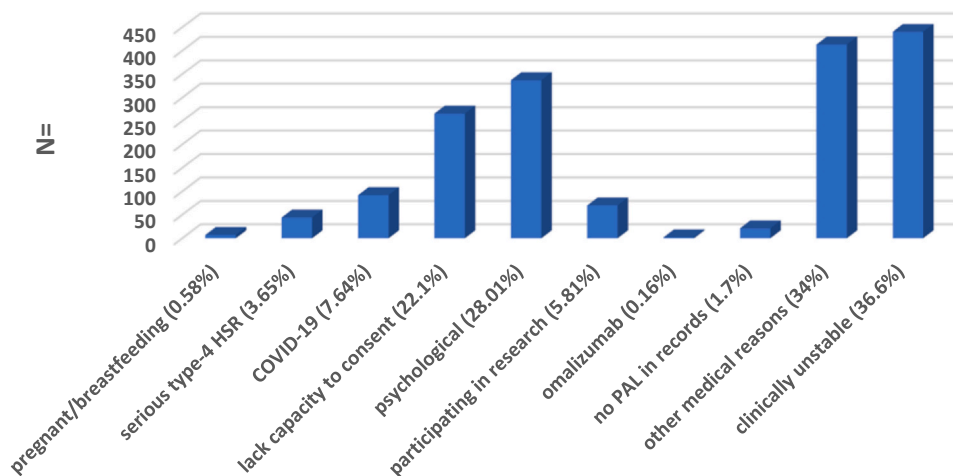


Fig. 3. Analysis of reasons for failure to progress from screening.

Table 5
Regression analysis of conversion from screening to consent in the patient pathway (dependent variable - consented).

		Not consented n = (%)	Consented n = (%)	OR (univariable)	OR (multivariable)
Hospital	Birmingham	690 (86.8)	105* (13.2)		
	Leeds	899 (90.8)	91 (9.2)	0.67 (0.49–0.90, p = 0.007)	0.83 (0.61–1.15, p = 0.264)
	Oxford	395 (83.7)	77 (16.3)	1.28 (0.93–1.76, p = 0.128)	1.68 (1.19–2.37, p = 0.003)
Clinical setting	AMU/ID	870 (96.7)	30 (3.3)		
	Haem-Oncol	318 (87.1)	47 (12.9)	4.29 (2.68–6.96, p < 0.001)	3.42 (2.08–5.70, p < 0.001)
	Pre-surgical	796 (80.2)	196 (19.8)	7.14 (4.88–10.81, p < 0.001)	5.53 (3.72–8.47, p < 0.001)
Age range (years)	< 30	89 (84.8)	16 (15.2)		
	30–39	125 (82.8)	26 (17.2)	1.16 (0.59–2.32, p = 0.674)	1.06 (0.53–2.17, p = 0.874)
	40–49	217 (84.8)	39 (15.2)	1.00 (0.54–1.93, p = 0.999)	0.97 (0.51–1.91, p = 0.932)
	50–59	290 (82.9)	60 (17.1)	1.15 (0.64–2.16, p = 0.646)	1.12 (0.61–2.15, p = 0.720)
	60–69	346 (85.4)	59 (14.6)	0.95 (0.53–1.78, p = 0.863)	0.97 (0.53–1.86, p = 0.925)
	70–79	441 (87.7)	62 (12.3)	0.78 (0.44–1.46, p = 0.418)	0.94 (0.52–1.79, p = 0.843)
	≥80	476 (97.7)	11 (2.3)	0.13 (0.06–0.28, p < 0.001)	0.23 (0.10–0.53, p = 0.001)
	Gender	Female	1268 (89.1)	155 (10.9)	
Male	716 (85.9)	118 (14.1)	1.35 (1.04–1.74, p = 0.022)	1.38 (1.05–1.81, p = 0.019)	

* Three patients were withdrawn from the study post-consent.

Table 6
Demographics of low-risk patients.

	All			AMU/ID unit			Pre-surgical			Haem/Oncol		
	B'ham	Oxford	Leeds	B'ham	Oxford	Leeds	B'ham	Oxford	Leeds	B'ham	Oxford	Leeds
N	60	52	43	6	13	2	34	32	38	20	7	3
Age years (median [IQR])	62.00 [49.00, 71.50]	54.50 [41.50, 68.25]	60.00 [47.50, 73.00]	61.50 [59.50, 72.50]	53.00 [39.00, 62.00]	67.00 [61.00, 73.00]	61.00 [51.75, 72.50]	51.00 [40.00, 65.50]	58.50 [47.25, 72.75]	63.00 [40.00, 69.50]	66.00 [56.00, 74.00]	63.00 [52.50, 68.00]
Gender												
M (%)	27 (45)	21 (40)	21 (49)	3 (50)	5 (39)	1 (50)	10 (29)	12 (38)	17 (45)	14 (70)	4 (57)	3 (100)
F (%)	33 (55)	31 (60)	22 (51)	3 (50)	8 (61)	1 (50)	24 (71)	20 (62)	21 (55)	6 (30)	3 (43)	0 (0)
Ethnicity												
White (%)	35 (58)	42 (81)	38 (84)	3 (50)	12 (92)	2 (100)	22 (65)	24 (75)	33 (87)	6 (86)	12 (92)	3 (100)
Non-White (%)	5 (8)	10 (19)	2 (5)	1 (17)	1 (8)	0 (0)	4 (12)	8 (25)	2 (5)	1 (14)	1 (8)	0 (0)
Not recorded (%)	20 (33)	0 (0)	3 (7)	2(33)	0 (0)	0 (0)	8 (24)	0 (0)	3 (8)	0 (0)	0 (0)	0 (0)

As a guide, not as a formal hypothesis test, there is little evidence of association between age and (hospital, setting) since a Kruskal-Wallis test yields p = 0.50 and a chi-squared test for gender by (hospital, setting) yields p = 0.10. Testing for ethnicity might be misleading due to small counts, especially multiple zeroes.

Table 7
Demographics of high-risk patients.

	All			AMU/ID unit			Pre-surgical			Haem/Oncol		
	B'ham	Oxford	Leeds	B'ham	Oxford	Leeds	B'ham	Oxford	Leeds	B'ham	Oxford	Leeds
N	33	25	46	4	4	1	19	19	43	10	2	2
Age years (median [IQR])	58.00 [53.50, 68.00]	60.50 [48.00, 64.50]	60.00 [48.75, 69.75]	71.50 [64.25, 75.75]	58.50 [40.25, 72.50]	55.00 [53.00, 64.00]	68.00 [53.00, 64.00]	60.00 [48.50, 63.00]	61.00 [48.00, 71.00]	57.00 [54.00, 61.75]	61.50	63.00
Gender												
M (%)	8 (24)	11 (44)	20(44)	1 (25)	2 (50)	0 (0)	4 (21)	8 (42)	19 (44)	3 (30)	1 (50)	1 (50)
F (%)	25 (76)	14 (56)	26 (56)	3 (75)	2 (50)	1(100)	15 (79)	11 (58)	24 (56)	7 (70)	1 (50)	1 (50)
Ethnicity												
White (%)	22 (67)	19 (76)	40 (87)	4 (100)	4 (100)	0 (0)	13 (68)	14 (74)	38 (88)	5 (50)	1 (50)	2(100)
Non-White (%)	3 (9)	6 (24)	3 (7)	0 (0)	0 (0)	0 (0)	1 (5)	5 (26)	3 (7)	2 (20)	1 (50)	0 (0)
Not recorded (%)	8 (24)	0 (0)	3 (7)	0 (0)	0 (0)	1 (100)	5 (26)	0 (0)	2 (5)	3 (30)	0 (0)	0 (0)

Table 8
DPC summary.

	All			AMU/ID unit			Pre-surgical			Haem/Oncol		
	B'ham	Oxford	Leeds	B'ham	Oxford	Leeds	B'ham	Oxford	Leeds	B'ham	Oxford	Leeds
Undergone DPC (n)	47	47	32	4	12	2	29	30	27	14	5	3
Opportunistic de-labelling	44	43	32	1	10	2	29	30	27	14	3	3
Therapeutic de-labelling	3	4	0	3	2	0				2		
De-labelled	45	46	31									
De-labelling rate	95.7%	97.9%	96.9%									

Table 9
Summary of adverse events.

	Total N	Immediate HSR	Non-immediate HSR [#]	Non-specific ^{##}	De-labelled N
Oxford	9 [*]	0	1	8	8
Leeds	2	0	0	2	1 [*]
Birmingham	16 [*]	0	2	13	14
Total	27	0	3	23	23

[#] Mild cutaneous.

^{##} Mild.

^{*} 1 patient SAE – unlikely to be related to DPC.

^{*} Not de-labelled as patient developed GIT side effects and did not complete 3 day DPC protocol.

elicit side chain reactivity. Tolerance of amoxicillin, therefore, effectively excludes allergy to the wider penicillin family. Current challenge test protocols are heterogeneous and have not been formally validated.¹⁹ We opted to administer a single dose of 500 mg amoxicillin to exclude type-I HSR followed by 250 mg twice daily for 3 days to exclude type-IV HSR based on our previous experience in specialist NHS allergy clinics. However, it is equally likely that a single dose amoxicillin challenge will suffice for most patients, prompting the recent recommendation against the use of multiple-day challenges by the American Academy of Allergy, Asthma and Immunology.²⁰

The high rate of successful de-labelling amongst 'low risk' patients employing a DPC in this study is concordant with findings from other countries.^{10,12} A systematic review involving a pooled analysis of 13 studies in 1202 'low risk' inpatients and outpatients reported that 96.5% cases were de-labelled via a DPC.¹⁰ There were no cases of serious type-I or type-IV HSRs. Forty-one out of 1202 (3.4%) developed mild type-I or IV HSRs. In a meta-analysis of 23 published studies (2001–2017) involving 5056 PALs, 97% and 86% were successfully de-labelled by DPC and skin tests *and* penicillin challenge respectively ($p < 0.001$); the higher rate in the former group was attributed to greater likelihood of participants with 'low risk' status.¹²

This study was conducted at three busy secondary care teaching hospitals across England over a wide geographical area making our findings generalisable for the UK NHS. Our screened sample included 11.6% patients of non-White ethnicity (UK population comprises 18% non-White ethnicity as per 2021 census) with a PAL. It is plausible that some patients from this group were not considered due to sub-optimal English language proficiency. There were 11.4% patients of non-White ethnicity amongst those who consented to participate.

Our data suggest that DPCs can be implemented by non-allergy specialist HCPs in the NHS provided relevant personnel are trained, there is a standard operating protocol in place alongside standardised antimicrobial stewardship policies supported by a local governance framework.

An important observation made in this study relates to the low conversion rate and elucidation of reasons for failed progression from screening to informed consent. Overall, conversion rate across all sites and all clinical settings was modest at 12% and particularly low (3.8%) in acute clinical settings. The odds for patient progression from screening-to-consent stage was significantly higher at Oxford. This variation between centres reflects numerous implementation factors that are further explored in detail in another manuscript.

Results of the implementation descriptions generated using the TIDIER checklist suggest that differences in patient demographics, case complexity and local service framework between centres may have contributed to the variations in experiences between the sites. Specifically, AMUs were spread across multiple wards at Leeds during the pandemic creating additional layers of complexity for research staff to contact clinical teams and patients. Screening was led by senior RPs (also independent non-medical prescribers) at

Oxford and Birmingham as opposed to RNs at Leeds. Irrespective of the professional background, it is plausible that differences in previous knowledge of antimicrobial stewardship and allergy, including familiarity with obtaining and interpreting a drug allergy history, as outlined, may also have contributed to differences in conversion rates between centres. Other non-Allergy specialist HCP led-studies using similar entry criteria to the SPACE study have highlighted large variations in conversion rates (studies summarised in Table 10). Patient demographics, case complexity including co-morbidities, clinical setting, views, perspectives and behavioural factors amongst HCPs and patients and local research governance framework may have contributed to the differences in conversion rates seen in these studies. Specifically, the risk stratification employed in this study broadly aligns to the PEN-FAST tool employed by Copaescu et al.²¹ in the PALACE trial, although our approach did not include a scoring system. Copaescu et al. deemed patients with psychological and neurological conditions as ineligible to be randomised, although did not list clinical instability and severe cardio-respiratory co-morbidities such as severe asthma, COPD or heart failure as an exclusion criterion. Given the feasibility nature of this non-allergy specialist led study, we opted to take a relatively more cautious and pragmatic approach.

Among the 1055 patients deemed potentially suitable at screening, 412 (39%) were not approached. This was due to logistical reasons such as patients being discharged or relocated to another clinical area, inability contact over telephone or research team not being able to contact patients in a timely manner due to time constraints.

Eight percent of 1203 ineligible patients did not meet study criteria due to pregnancy, breast feeding and concomitant COVID-19 infection. Some of these patients could have been approached for risk stratification at a later time point in 'real world' clinical practice. Lack of capacity to give informed consent and underlying psychiatric/psychological illness prevented 22% and 28% of patients respectively from undergoing DPC but may be considered in 'real world' clinical practice akin to other medical and surgical interventions under an appropriate governance framework, including support from professional translators for those with sub-optimal English language proficiency thereby increasing equity and equality of care. Thirty-six percent of cases with a PAL were deemed clinically unstable and 34% had other medical reasons and could not be considered for participation. For examples, there were cases across the three participating sites where patients were deemed medically unsuitable at the point of consideration due to confusion, delirium, uncontrolled blood pressure, cardiac arrhythmia, asthma/COPD exacerbation, heart failure, gastro-intestinal problems, ethanol toxicity, frailty, etc., but may have been suitable at a later time point in a 'real world' setting where there is a mechanism for follow up.

Our findings suggest a multi-pronged approach is needed in the UK NHS to maximise uptake of DPC. This includes but is not limited to contacting patients at an appropriate and optimal time point after their clinical condition has improved (possibly after discharge), provision of

Table 10
Summary of conversion rates reported in other non-allergy HCP-led studies with similar entry criteria.

Author, year, country	Number of study centres	Conversion rate	Total considered in the study	Comments
Brayson J et al., 2023, England (CATALYST study) ¹⁶	1	43%	304	Pharmacist-led in medical and surgical wards. List of reasons not provided by authors
Sneddon J et al., 2021, Scotland ¹⁷	1	92%	112	Infectious Diseases team led. Inpatients from respiratory and medical admissions unit
Chua KYL, 2020; Australia ¹⁸	2	28.6%	1225	Reasons for failure to progress in study pathway: High risk – 54%; Low risk – 46%. Amongst low risk - declined (29.8%), clinician's refusal (5.3%), unwell (18.3%), antihistamines/high dose steroids (8.2%), discharged (34.6%), and others (3.8%)
Devchand M et al., 2019, Australia ²²	1	34%	309	Pharmacist-led. Reasons for failure to progress in study pathway: patient not available at ward round (30%), acutely unwell (8.9%), confusion/cognitive impairment (18.2%), in ICU/spinal/Paediatric unit (11.3%), palliated (2%) and serious reaction (nephritis; 0.5%)
Stollings JL et al., 2023, USA ²⁶	1	9%	285	Study involving COVID-19 positive patients in medical ICU. Reasons for failure to progress in study pathway: unable to provide history, haemodynamic instability, on mechanical or non-invasive ventilation
Koo G et al., 2022, USA ²⁵	1	28.6%	839	Non-COVID-19 patients in ICU. Reasons for failure to progress in study pathway: unable to provide history, haemodynamic instability, on mechanical or non-invasive ventilation
Du Plessis T et al., 2019, New Zealand ²⁷	1	92%	274	Pharmacist-led. All inpatients in a tertiary care referral hospital were considered except mental health ward and theatre day admission unit. Reasons for failure to progress in study pathway: Admitted under mental health (46%), language barrier (29%), cognitive impairment (12.5%, declined (12.5%))
Copaescu AM et al., USA, Canada and Australia ²¹	6	60%	643	6 specialised centres involving elective clinical settings; N = 643 screened and patients risk stratified with PEN-FAST tool. Open-label RCT with 2 arms (DPC [N = 190] and skin tests ± supervised oral penicillin challenge [N = 192]). Study demonstrated non-inferiority of DPC. Reasons for failure to progress: high-risk 13%, deemed unsuitable by investigator ([eg: neurological, psychological conditions] 11%); previous history of significant pharmacological type A or B adverse drug reactions (4%), pregnancy (1%), unclear history (0.9%), concurrent antihistamine treatment (0.1%), declined to participate (3.2%) and reason unknown (6.7%)

culturally tailored supportive measures for those from ethnic minority groups with suboptimal English language proficiency and an appropriate governance framework for those unable to give informed consent. These approaches would facilitate efforts to make the intervention more equitable.

This study has limitations. First, the sample size for DPCs was moderate at 126. However, this was a feasibility study, and the primary aim was not to investigate safety. Second, very few patients underwent DPC in an acute clinical setting. We reviewed conversion rates 3–4 months after commencement of recruitment, recognised the very low conversion rate in an acute clinical setting, and thereafter focused efforts on elective clinical settings for the remaining study period in the interest of achieving the target of 122 DPCs. Whilst there are data from USA, Australia and NZ and some evidence from the UK^{16,17,22} regarding feasibility and safety of DPCs undertaken in busy inpatient settings,^{18,23–26} further data are needed from the UK due to differences in service and governance framework. Third, it was not within the scope of this study to investigate the impact of de-labelling on antimicrobial stewardship, or to conduct long term follow up and confirm whether patient records were updated in primary care following formal written communication to patient's general practitioner. Although we had good geographical coverage, all study sites were large teaching hospitals and findings may potentially differ in district general hospitals.

This study adds to the growing body of evidence attesting to the safety and simplicity of a DPC for 'low-risk' patients with a spurious PAL. By demonstrating safe and effective delivery of a de-labelling service by HCPs without a background in allergy, our study provides a framework for adoption of de-labelling beyond the UK NHS, including in resource-limited settings.

CRediT authorship contribution statement

Mamidipudi Thirumala Krishna: Conceptualisation, funding acquisition, study protocol, chief investigator, site principal investigator, drafting manuscript and manuscript editing. Rashmeeth Bhogal: Lead clinical pharmacist, pre-study workshop lead, screening, risk stratification, DPC, data validation, manuscript review and approval. Bee Yean Ng: Screening, risk stratification, DPC, data validation, manuscript review and approval. Kornelija Kildonaviciute: Screening, risk stratification, DPC, data validation, manuscript review and approval. Yogini H Jani: Conceptualisation, funding acquisition, study protocol, manuscript review and approval. Iestyn Williams: Conceptualisation, funding acquisition, study protocol, manuscript review and approval. Jonathan A. T. Sandoe: Conceptualisation, funding acquisition, study protocol, manuscript review and approval. Rachel Pollard: Risk stratification, DPC, data validation, manuscript review and approval. Nicola Jones: Risk stratification, DPC, data validation, manuscript review and approval. Louise Dunsmure: Local study management, manuscript review and approval. Neil Powell: Conceptualisation, funding acquisition, study protocol, manuscript review and approval. Chidanand Hullur: Risk stratification, DPC, data validation, manuscript review and approval. Ariyur Balaji: Risk stratification, DPC, data validation, manuscript review and approval. Catherine Moriarty: Local study management, manuscript review and approval. Beverley Jackson: Local study management, screening, risk stratification, DPC, manuscript review and approval. Amena Warner: Conceptualisation, funding acquisition, study protocol, manuscript review and approval. Ron Daniels: Conceptualisation, funding acquisition, study protocol, manuscript review and approval. Robert West: Conceptualisation, funding

acquisition, study protocol, data validation, statistical analysis, drafting manuscript, manuscript review and approval. Caroline Thomas: Data validation, site principal investigator, manuscript review and approval. Siraj A. Misbah: Conceptualisation, funding acquisition, study protocol, site principal investigator, drafting manuscript, manuscript review and approval. Louise Savic: Conceptualisation, co-chief investigator, funding acquisition, study protocol, manuscript review and approval.

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COI declaration

- M.T.K. received research funds from NIHR RfPB, MRC C1c, GCRF, FSA and University of Birmingham outside this work. His department at UHB has received educational grants for PracticAllergy course from ALK Abello, Allergy Therapeutics, MEDA, Thermo Fisher Scientific and other pharmaceutical companies over the years. He is Chair of Equality, Diversity and Inclusion working group of BSACI, co-author for BSACI guidelines on penicillin allergy and an associate editor for Clinical Experimental Allergy.
- R.D. delivered paid consultancy services to Baxter medical. He has a salaried position as chief executive of UK Sepsis Trust.
- R.B. received funding or honoraria for conference attendance, Advisory boards, lectures and training from Pfizer and Menarini. Senior Editor for JAC-AMR (BSAC journal).
- N.P. is a NIHR/HEE CDRF studying non-allergist penicillin allergy de-labelling in secondary care (Clinical Doctoral Research Fellowship). He is Co-lead on the BSAC MOOC on non-allergist penicillin allergy de-labelling (British Society Antimicrobial Chemotherapy Massive Open Online Community).
- S.A.M. is National Clinical Director for the Blood and Infection Programme of Care, NHS England.
- J.A.T.S. has research funding from the National Institute for Health and are Research and Wellcome Trust in relation to penicillin allergy. J.S. is a member of the British Society for Allergy and Clinical Immunology allergy working party. J.S. is Co-lead on the BSAC MOOC on non-allergist penicillin allergy de-labelling (British Society Antimicrobial Chemotherapy Massive Open Online Community) and a BSAC council member.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.jinf.2024.01.015](https://doi.org/10.1016/j.jinf.2024.01.015).

References

- Shenoy ES, Macy E, Rowe T, Blumenthal KG. *Evaluation and management of penicillin allergy: a review*. JAMA 2019;**321**(2):188–99.
- West RM, Smith CJ, Pavitt SH, Butler CC, Howard P, Bates C, 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):2075–82.
- Lee CE, Zembower TR, Fotis MA, Postelnick MJ, Greenberger PA, Peterson LR, et al. *The incidence of antimicrobial allergies in hospitalized patients: implications regarding prescribing patterns and emerging bacterial resistance*. Arch Intern Med 2000;**160**(18):2819–22.
- Sacco KA, Bates A, Brigham TJ, Imam JS, Burton MC. *Clinical outcomes following inpatient penicillin allergy testing: a systematic review and meta-analysis*. Allergy 2017;**72**(9):1288–96.
- Macy E, Ngor EW. *Safely diagnosing clinically significant penicillin allergy using only penicilloyl-poly-L-lysine, penicillin, and oral amoxicillin*. J Allergy Clin Immunol Pr 2013;**1**(3):258–63.
- Blumenthal KG, Lu N, Zhang Y, Li Y, Walensky RP, Choi HK. *Risk of meticillin resistant Staphylococcus aureus and Clostridium difficile in patients with a documented penicillin allergy: population based matched cohort study*. BMJ 2018;**361**:k2400.
- 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):790–6. PubMed PMID: 24188976.
- Mirakian R, Ewan PW, Durham SR, Youlten LJ, Dugue P, Friedmann PS, et al. *BSACI guidelines for the management of drug allergy*. Clin Exp Allergy 2009;**39**(1):43–61.
- Warner JO, Kaliner MA, Crisci CD, Del Giacco S, Frew AJ, Liu GH, et al. *Allergy practice worldwide: a report by the World Allergy Organization Specialty and Training Council*. Int Arch Allergy Immunol 2006;**139**(2):166–74. PubMed PMID: 16388197.
- Cooper L, Harbour J, Sneddon J, Andrew Seaton R. *Safety and efficacy of de-labelling penicillin allergy in adults using direct oral challenge: a systematic review*. JAC-Antimicrob Resist 2021;**3**(1):1–10. <https://doi.org/10.1093/jacamr/dlaa123>
- Savic L, Ardern-Jones M, Avery A, Cook T, Denman S, Farooque S, et al. *BSACI guideline for the set-up of penicillin allergy de-labelling services by non-allergists working in a hospital setting*. Clin Exp Allergy 2022;**52**(10):1135–41.
- DesBiens M, Scalia P, Ravikumar S, Glick A, Newton H, Erinne O, et al. *A closer look at penicillin allergy history: systematic review and meta-analysis of tolerance to drug challenge*. Am J Med 2020;**133**(4):452–462 e4. PubMed PMID: 31647915. Epub 20191021.
- Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. *Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide*. BMJ 2014;**348**:g1687.
- Staniszewska S, Brett J, Simera I, Seers K, Mockford C, Goodlad S, et al. *GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research*. BMJ 2017;**358**:j3453.
- Mohamed OE, Beck S, Huissoon A, Melchior C, Heslegrave J, Baretto R, et al. *A retrospective critical analysis and risk stratification of penicillin allergy delabelling in a UK specialist regional allergy service*. J Allergy Clin Immunol Pr 2019;**7**(1):251–8.
- Brayson J, Barrett S, Baqir W, Campbell D, Oswald T, Ellis S, et al. *CATALYST: challenging antibiotic allergy status*. J Antimicrob Chemother 2023;**78**(5):1241–4. <https://doi.org/10.1093/jac/dkad081>
- Sneddon J, Cooper L, Ritchie N, Steele C, Spears M, McEwen J, et al. *An algorithm for safe de-labelling of antibiotic allergy in adult hospital in-patients*. Clin Exp Allergy 2021;**51**(9):1229–32.
- Chua KYL, Vogrin S, Bury S, Douglas A, Holmes NE, Tan N, et al. *The penicillin allergy delabelling program: a multicenter whole-of-hospital health services intervention and comparative effectiveness study*. Clin Infect Dis 2020;**73**(3):487–96. <https://doi.org/10.1093/cid/ciaa653>
- Bhogal R, Hussain A, Savic L, Misbah SA, Balaji A, Hullur C, et al. *Heterogeneity in direct oral penicillin challenge protocols in penicillin allergy de-labelling*. Infect Prev Pr 2022;**4**(3):100185.
- Khan DA, Banerji A, Blumenthal KG, Phillips EJ, Solensky R, White AA, et al. *Drug allergy: a 2022 practice parameter update*. J Allergy Clin Immunol 2022;**150**(6):1333–1393.
- Copaescu AM, Vogrin S, James F, Chua KYL, Rose MT, De Luca J, et al. *Efficacy of a clinical decision rule to enable direct oral challenge in patients with low-risk penicillin allergy: the PALACE randomized clinical trial*. JAMA Intern Med 2023;**183**(9):944–52.
- Devchand M, Kirkpatrick CMJ, Stevenson W, Garrett K, Perera D, Khumra S, 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.
- Blumenthal KG, Shenoy ES, Wolfson AR, Berkowitz DN, Carballo VA, Balekian DS, et al. *Addressing inpatient beta-lactam allergies: a multihospital implementation*. J Allergy Clin Immunol Pr 2017;**5**(3):616–625 e7.
- Trubiano JA, Vogrin S, Chua KYL, Bourke J, Yun J, Douglas A, et al. *Development and validation of a penicillin allergy clinical decision rule*. JAMA Intern Med 2020;**180**(5):745–52.
- Koo G, Stollings JL, Lindsell C, Dear ML, Kripalani S, Nelson GE, et al. *Low-risk penicillin allergy delabeling through a direct oral challenge in immunocompromised and/or multiple drug allergy labeled patients in a critical care setting*. J Allergy Clin Immunol Pr 2022;**10**(6):1660–1663 e2. PubMed PMID: 35131513. PubMed Central PMCID: PMC9188986. Epub 20220205.
- Stollings JL, Koo G, Lindsell CJ, Dear ML, McCoy A, Rice TW, et al. *Risk-stratified management to remove low-risk penicillin allergy labels in the patients with COVID-19 in the intensive care unit*. J Allergy Clin Immunol Pr 2023;**11**(2):632–5.
- 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;**74**(5):1438–46.