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10 **A randomised evaluation of an antibiotic allergy assessment tool for supporting penicillin allergy de-**
11 **labelling by non-allergists.**

12 **Penicillin allergy de-labelling by non-allergists**

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34 Key messages

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- AAAT use significantly improved performance in correct phenotyping and management of reported penicillin allergies.
 - There remains a risk of error in managing penicillin allergies with the AAAT by non-allergists.
 - De-labelling tools should be incorporated into a wider allergy training strategy of non-allergists

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40 To the Editor

41 More than 90% of patients with penicillin allergy recorded are found not to be allergic after formal allergy
42 testing, and can safely tolerate penicillin.¹ Patients with penicillin allergy recorded are often prescribed
43 second-line antibiotics which are more costly,² can be less effective, and associated with a greater risk of
44 adverse reactions.³

45 There is an accumulating body of evidence demonstrating the safety and efficacy of removing incorrect
46 penicillin allergy records (de-labelling) following risk assessment and observed oral penicillin challenge
47 without the need for prior skin testing.⁴ The development and validation of pathways that enable non-
48 allergists to manage and remove incorrect penicillin allergy labels have the potential to vastly increase de-
49 labelling in both outpatient and hospital settings.

50 Devchand *et al.* used eight vignettes, derived from real patients with a self-reported penicillin allergy who
51 had undergone formal allergy testing, to validate a beta-lactam antibiotic allergy assessment tool
52 (AAAT).^{5,5}

53 This study aimed to determine whether non-allergy trained NHS healthcare workers were able to use the
54 AAAT to correctly phenotype and manage the same eight clinical vignettes in the study by Devchand *et al.*

55 The study was set across two stages in three district general hospitals in South West England. Hospital
56 email lists were used to identify participants from the following staff groups: pharmacists, non-medical
57 prescribers, consultants, associate specialists, foundation doctors, core trainee doctors and registrars.
58 Two surveys were developed in which the vignettes were identical; one survey directed participants to
59 use the AAAT, while the other did not provide the AAAT. In stage one, participants from a single hospital
60 were grouped by job role and then randomised to either the AAAT group or without AAAT group using the
61 RAND function in excel.⁶ In stage two, participants at two further hospitals were identified and invited to
62 complete the survey using the AAAT. All participants were emailed weekly over four weeks.

63 NHS ethical approval was not required as the study did not meet the Health Research Authority definition
64 for research, or the requirements for NHS Research Ethics Committee approval.

65 The AAAT gives six possible phenotypes: severe immediate hypersensitivity, non-severe immediate
66 hypersensitivity, severe delayed hypersensitivity, non-severe delayed hypersensitivity, other immune-
67 mediated, and unlikely to be significant. Each phenotype was assigned a corresponding management
68 option: direct de-label (DDL, direct removal of reported allergy record), supervised direct oral challenge
69 (DOC; removal of allergy record following uneventful antibiotic oral provocation challenge under

supervision), and outpatient antibiotic allergy assessment (OAAS).⁵ The AAAT was modified so that phenotypes requiring formal skin testing were assigned to OAAS to reflect local service provision. Incorrect management responses were categorised as either a major or a minor error. A major error was defined as a situation where management might result in patient harm and included the selection of DDL or DOC when OAAS was indicated. A minor error was considered an error that was unlikely to cause patient harm but result in a more costly or inconvenient management. The categorisation of errors was determined by consensus among the study authors. A mean total score was calculated (composite of phenotype score + management score (both out of a possible eight) – number of major errors) and used in a multivariable analysis accounting for use of the AAAT, study centre and job role.

The overall response rate was 515/1954 (26.4%). After removal of incomplete surveys, the response rate in Centre A was 70/359 (19.4%) with the AAAT and 88/358 (25%) without the AAAT, and 91/490 (18.6 %) and 151/747 (17.2%) for Centres B and C respectively.

In centre A, participants were significantly better at assigning correct phenotype (5.22 vs 6.70; $p < 0.001$) and correct management (5.70 vs 7.16; $p < 0.001$) with use of the AAAT than without (table I). Use of the AAAT also demonstrated a significant reduction in major errors (1.52 vs 0.51; $p < 0.001$) (table I). There was no significant difference between phenotype, management or major error scores between centres using the AAAT (table I).

A total score combined of phenotype score, management score and major errors was used in a multivariate analysis to assess variables of job role, study centre and use of AAAT. Mean total score was significantly greater with the AAAT (13.4/16) than without (9.4/16), associated with a four-unit improvement ($\beta = 4.03$; 95CI=3.46-4.60; $p < 0.001$). Consultants achieved the highest mean total score at 12.7, followed by non-consultant doctors (12.5($\beta = -0.35$; 95CI=-0.89-0.20; $p = 0.209$)), pharmacists (12.4($\beta = -0.42$; 95CI=-1.13-0.30; $p = 0.253$)) and non-medical prescribers (12.0($\beta = -0.42$; 95CI=-1.13-0.30; $p = 0.253$)). After accounting for use of the AAAT there was no significant difference in performance between Centres A and B ($\beta = 0.11$; 95CI=-0.64-0.86; $p = 0.776$), or Centres A and C ($\beta = 0.12$; 95CI=-0.57-0.81; $p = 0.732$).

Correct response, major error and minor error rates for each case study are displayed by study centre in table II. In Case 1, participants were consistently poor at assigning the correct phenotype, choosing “delayed hypersensitivity (non-severe)” instead of “unlikely to be significant” but assigned the correct

99 management most of the time because management was the same for both phenotypes. Cases 7 and 8
100 incurred the highest major error rates across all three centres and job roles.

101 Our data show that an AAAT, used by non-allergist healthcare workers, significantly improved accuracy of
102 assigning phenotype and appropriate management and reduced the risk of major error. Overall accuracies
103 of phenotyping and management with the AAAT were comparable to those of Devchand *et al.*⁵ Despite
104 improved performance with the AAAT, all job roles incurred major errors in management choice. The risk
105 of mismanagement therefore remains a barrier to the removal of penicillin allergy labels by non-allergists
106 without additional training.

107 Multivariable analysis of mean total scores suggests that performance with the AAAT was consistent
108 across all three centres. Little evidence of significant differences was found with performance across job
109 categories. Although we felt that the AAAT provided clear instructions that the management of
110 immediate diffuse rash (case 7) and a recent delayed diffuse rash (case 8) should be OAAS, this advice was
111 overruled by many participants who incorrectly chose DOC or DDL. The AAAT is limited in that it doesn't
112 prompt the assessor to ask the right questions to ensure an accurate allergy history is taken from the
113 patient and this may limit the safety of the AAAT in practise. An allergy assessment and de-labelling
114 algorithm which incorporates both the questions and the decision may better facilitate non-allergist
115 assessment and safe de-label of patients with an incorrect penicillin allergy label.⁷

116 In order to mitigate the risk of incorrect de-labelling, a broader clinical framework is required that
117 encompasses healthcare worker training, defined governance structures and a safe clinical environment.⁸
118 A study looking at healthcare worker attitudes towards the management of penicillin allergies found a
119 lack of confidence, support structures, and formal training to be potential barriers to healthcare workers
120 assessing patients with penicillin allergies.⁹

121 Lin *et al.* report on their use of physician education as part of their antibiotic allergy de-labelling
122 intervention delivered by physicians. Forty-two patients were given an oral penicillin challenge of which
123 40 patients (95%) had an uneventful challenge and two (5%) patients developed a non-severe skin
124 reaction after drug challenge.¹⁰ A similar educational intervention may reduce the risk of major errors
125 with the AAAT. Additionally, interventions need to address the problem of acquisition of incorrect allergy
126 labels.

127 Our study has several limitations. Incomplete surveys were excluded due to the risk of duplication where
128 participants reattempted the survey after initially not completing the survey, which may lead to response
129 bias. Hospital email lists were used which may have contained individuals not targeted for the study (e.g.

healthcare workers without direct patient contact) and also may contain email addresses of individuals no longer working at the hospital, both may have contributed to the low response rate. Due to the low response rate the data may not be representative of the study population, as those with an interest or expertise in this topic may be more likely to complete the survey. The use of vignettes does not account for the varying accuracy of patient recall in allergy assessment and the unreliability of allergy documentation which highlights the need for thorough allergy training pathways that incorporate allergy history taking, improved documentation of allergic reactions and decision tools that default to the lowest risk option if there is uncertainty. Major and minor classification of errors has to our knowledge not been used in this context before, and while the distinction was made by overall consensus among the study authors there was diversity of opinion on the categorisation of selecting DDL when DOC was indicated. For the purposes of this study we categorised this as a minor error as the risk of patient harm was low. In practice the patient would receive a full dose with either option; the difference would be whether it was a planned DOC or simply receiving the first dose of a treatment course.

The AAAT is a useful component of penicillin allergy de-labelling programmes to identify patients at low risk of allergy. The persistence of major errors when using the AAAT indicates that the AAAT alone would not be sufficient and suggests the need for validated training programmes that could demonstrate zero major errors in decisions around penicillin allergy de-labelling so that this important antibiotic stewardship intervention can be delivered safely.

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155 **Conflict of interest statement**

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159 **Data availability**

160 The data that support the findings of this study are available from the corresponding author upon
161 reasonable request.

162 **Author Contributions**

163 Conceptualisation: RO, JS, AFW, MW, NP; Data collection: RO, MS, RB; Statistical analysis RW; Reviewing
164 and editing: all authors; Supervision: NP. All authors have read and agreed to the published version of the
165 manuscript.

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Tables

Table I. Mean participant scores for correct phenotype, correct management choice, major errors, and total score by randomised group and by centre.

		Centre A			AAAT			
		No AAAT	AAAT	p -value	Centre A	Centre B	Centre C	p-value
n		88	70		70	91	151	
Job role (%)	Consultant	40 (45.5)	31 (44.3)	0.943	31 (44.3)	41 (45.1)	52 (34.4)	0.094
	Non-consultant doctor	29 (33.0)	26 (37.1)		26 (37.1)	32 (35.2)	53 (34.4)	
	Non-medical prescriber	6 (6.8)	4 (5.7)		4 (5.7)	4 (4.4)	23 (15.2)	
	Pharmacist	13 (14.8)	9 (12.9)		9 (12.9)	14 (15.4)	24 (15.9)	
Phenotype	mean (SD)	5.55 (1.31)	6.70 (1.12)	<0.001	6.70 (1.12)	6.70 (0.89)	6.81 (0.98)	0.640
Management	mean (SD)	5.70 (1.24)	7.16 (0.93)	<0.001	7.16 (0.93)	7.25 (1.15)	7.13 (1.18)	0.692
Major errors	mean (SD)	1.52 (1.05)	0.51 (0.79)	<0.001	0.51 (0.79)	0.49 (0.79)	0.57 (0.94)	0.788
Total score	mean (SD)	9.40 (2.73)	13.34 (2.15)	<0.001	13.34 (2.15)	13.46 (2.15)	13.36 (2.49)	0.935

Table II. Correct response rate, major and minor management error rates for each case study using the AAAT.

	Centre A (n = 70)				Centre B (n = 91)				Centre C (n = 151)			
	Correct phenotype (%)	Correct management (%)	Major management error (%)	Minor management error (%)	Correct phenotype (%)	Correct management (%)	Major management error (%)	Minor management error (%)	Correct phenotype (%)	Correct management (%)	Major management error (%)	Minor management error (%)
Case 1	42	86	0	14	39	87	0	13	43	84	0	16
Case 2	97	93	0	7	96	92	0	8	97	95	0	5
Case 3	100	99	1	0	97	98	2	0	97	98	2	0
Case 4	90	92	8	0	95	97	3	0	88	93	7	0
Case 5	90	94	5	0	91	95	5	0	94	95	5	0
Case 6	93	74	0	6	98	96	0	4	98	91	0	9
Case 7	71	88	13	0	73	83	17	0	71	81	19	0
Case 8	82	72	28	0	83	77	23	0	76	76	24	0