# Penicillin allergy assessment pathway versus usual clinical care for primary care patients with a penicillin allergy record in the UK (ALABAMA): an open-label, multicentre, randomised controlled trial

*Jonathan A T Sandoe*, Shadia Ahmed, Kelsey Armitage, Chris Bates, Rebecca Bestwick, Jenny Boards, Christopher C Butler, Johanna Cook, Joanne Fielding, Ushma Galal, Philip Howard, Daniel Howdon, Sam Mort, Ruben Mujica-Mota, Alina Negut, Catherine E Porter, Neil Powell, Marta Santillo, Ravishankar Sargur, Sinisa Savic, Sarah Tonkin-Crine, Marta Wanat, Robert M West, Miaoqing Yang, Ly-Mee Yu, Susan H Pavitt*, on behalf of the ALABAMA Trial Research Group†*

## Summary

**Background** Penicillin allergy labels in medical records are common, often incorrect, and associated with increased antibiotic use and worse health outcomes. We aimed to establish whether a penicillin allergy assessment pathway initiated in primary care could safely improve use of penicillins.

**Methods** ALABAMA was a multicentre, open-label, randomised pragmatic trial with embedded process and cost-effectiveness evaluations. Participants came from 51 UK general practices and testing took place at four UK hospital sites (Leeds Teaching Hospitals NHS Trust, Sheffield Teaching Hospitals NHS Foundation Trust, Royal Cornwall Hospitals NHS Trust, and Bradford Teaching Hospitals NHS Foundation Trust). Eligible participants were aged 18 years or older, provided informed consent, had a record of penicillin allergy or sensitivity in their electronic medical records, had received an antibiotic prescription in the previous 24 months, and were outpatients at the time of recruitment. Participants were randomly assigned (1:1) by the research team to either a penicillin allergy assessment pathway or usual clinical care, by use of a secure, web-based system. The primary outcome was the proportion of participants who received at least one prescription for a penicillin for conditions for which a penicillin is first-line therapy, up to 12 months after random assignment. The original primary outcome was changed on July 12, 2023, from treatment response failure to penicillin prescribing due to slow recruitment caused by the COVID-19 pandemic. The primary analysis population was defined as all randomly assigned participants for whom outcome data were available. Safety was assessed in the as-treated population (ie, participants analysed by the intervention they received). The study was registered with ISRCTN, ISRCTN20579216, and ClinicalTrials.gov, NCT04108637, and is completed.

**Findings** Between Sept 17, 2019, and Oct 9, 2023, 1616 participants expressed interest and 823 were enrolled and randomly allocated (411 to the penicillin allergy assessment pathway and 412 to usual clinical care). 401 penicillin allergy assessment pathway and 410 usual clinical care participants were included in the primary analysis. 584 (72%) of 811 patients were female and 227 (28%) were male, the mean age was 55 years (SD 15·6), 786 (97%) of 811 patients were White, and 13 (2%) were non-White. 72 (18%) of 401 participants in the penicillin allergy assessment pathway group and 14 (3%) of 410 participants in the usual clinical care group were prescribed at least one course of a penicillin for a condition for which it was first-line therapy during follow-up (adjusted relative risk 5·27, 95% CI 3·03 to 9·18; adjusted risk difference 14·21%, 9·92 to 18·49). 83 adverse events occurred in 73 participants in the 28 days after allergy testing; one event was severe and probably related to the intervention. In the as-treated population, 27 (7%) of 365 participants who received the penicillin allergy assessment pathway and 34 (8%) of 446 participants who received usual clinical care had at least one serious adverse event during the 1-year follow-up. There were no deaths related to the intervention.

**Interpretation** Our data suggest that the penicillin allergy assessment pathway can increase prescription of narrow-spectrum penicillins with few signals of harm, indicating its potential in antibiotic stewardship.

**Funding** National Institute for Health and Care Research.



*Lancet Prim Care* 2025; 1: 100006

Published Online July 14, 2025 https://doi.org/10.1016/j.lanprc.2025.100006

See Comment https://doi.org/10.1016/j.lanprc.2025.100013

*Contributed equally

†Members are listed at the end of the Article and in the appendix (p 3)

**Leeds Institute of Medical Research, School of Medicine, University of Leeds, Leeds, UK** (J A T Sandoe PhD, S Ahmed MBChB); **Leeds Teaching Hospitals NHS Trust, Leeds, UK** (J A T Sandoe, S Ahmed); **Oxford Primary Care Clinical Trials Unit, Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK** (K Armitage BSc, Prof C C Butler FMedSci, J Cook MSc, U Galal MSc, S Mort PGCert, Prof L-M Yu DPhil); **The Phoenix Partnership, Horsforth, UK** (C Bates PhD); **Leeds Institute of Health Sciences, University of Leeds, Leeds, UK** (R Bestwick MSc, D Howdon PhD, R Mujica-Mota PhD, Prof R M West DPhil, M Yang PhD); **SMILE AIDER PPIE Forum, Dental Translational and Clinical Research Unit, NIHR Leeds Clinical Research Facility, School of Dentistry, University of Leeds, Leeds, UK** (J Boards); **Dental Translational and Clinical Research Unit, School of Dentistry, University of Leeds, Leeds, UK** (J Fielding BA Hons, C E Porter PGCert, Prof S H Pavitt PhD); **NHS England North-East and Yorkshire, Newcastle, UK** (Prof P Howard BPharm); **School of Healthcare, University of Leeds, Leeds, UK** (Prof P Howard);

**Infectious Diseases Department, Bradford Teaching Hospitals NHS Foundation Trust, Bradford, UK** (A Negut PhD); **Pharmacy Department, Royal Cornwall Hospital NHS Trust, Truro, UK** (N Powell MSc); **Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK** (M Santillo PhD, S Tonkin-Crine PhD, M Wanat PhD); **Clinical Immunology and Allergy Unit, Northern General Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK** (R Sargur FRCPath); **Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK** (Prof S Savic PhD); **Department of Clinical Immunology and Allergy, St James's University Hospital, Leeds, UK** (Prof S Savic); **National Institute for Health Research Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance, University of Oxford–UK Health Security Agency, Oxford, UK** (S Tonkin-Crine)

Correspondence to: Dr Jonathan A T Sandoe, Leeds Institute of Medical Research, School of Medicine, University of Leeds, Leeds LS2 9JT, UK
**j.sandoe@leeds.ac.uk**

See Online for appendix

## Introduction

Population-based studies indicate that 5–8% of adults and children have a penicillin allergy label in their medical records.[1–3] Penicillin allergy labels result in less penicillin use and increased non-penicillin antibiotic prescribing,[3–5] but there are associated negative health outcomes, including increased rates of treatment failure and mortality.[3,6] Less than 10% of patients with penicillin allergy labels are truly allergic when formally assessed;[7–10] consequently, millions of people have reduced access to penicillins due to incorrect penicillin allergy labels.[3] A patient can be incorrectly labelled as having a penicillin allergy for various reasons, including symptoms of the index infection being mistaken for allergic reactions (eg, rashes), side-effects being mislabelled as allergic reactions, health record systems not easily allowing distinction between side-effects and allergic reactions, and true allergies waning over time.

Incorrect penicillin allergy labels can be corrected (delabelling) by a process of formal allergy assessment; the gold-standard test with which to establish tolerance to penicillins is a drug challenge test (also known as drug provocation test, oral challenge test, or direct oral challenge test). In practice, this test usually involves oral administration of the test penicillin (an oral challenge test). Although numerous observational studies have indicated that penicillin allergy assessment and delabelling are feasible in individuals at low risk of a serious allergic reaction,[11] to our knowledge, no randomised trials have been done in adults in primary care to establish or quantify the effect on antibiotic prescribing and patient health outcomes. Aside from specialists, a range of non-specialists are involved in penicillin allergy assessments, including pharmacists, nurses, doctors, nurse practitioners, and physician associates.[11]

The Allergy Antibiotics and Microbial Resistance (ALABAMA) trial aimed to evaluate whether a penicillin allergy assessment pathway was safe and effective in removing incorrect penicillin allergy labels (delabelling) and improving antibiotic prescribing and health outcomes versus usual clinical care.

## Methods

### Study design

ALABAMA was a multicentre, open label, randomised pragmatic trial with a nested pilot study and embedded process and cost-effectiveness evaluations. Participants came from 51 English general practices and testing took place at four UK National Health Service (NHS) hospital sites (Leeds Teaching Hospitals NHS Trust, Sheffield Teaching Hospitals NHS Foundation Trust, Royal Cornwall Hospitals NHS Trust, and Bradford Teaching Hospitals NHS Foundation Trust). Testing began in Leeds Teaching Hospitals NHS Trust in January, 2020, in Sheffield Teaching Hospitals NHS Foundation Trust in October, 2022, in Royal Cornwall Hospitals NHS Trust in February, 2023, and in Bradford Teaching Hospitals NHS Foundation Trust in November, 2022.

### Research in context

#### Evidence before this study

We searched MEDLINE and Embase between Jan 1, 2010, and Dec 31, 2019, to identify general population-based studies in English, on the prevalence of and risk factors for penicillin allergy; the effect of penicillin allergy on penicillin prescribing; and randomised trials of penicillin allergy assessment versus usual clinical care or no penicillin allergy assessment control. We used the search terms "penicillin allergy", "beta-lactam allergy", "antibiotic allergy", "randomised trial", "prevalence", "penicillin", "beta-lactam", "epidemiology", and "risk factors". Our search identified few general population-based studies, with rates of penicillin allergy of 6–8%. We did not identify any adequately powered trials of penicillin allergy assessment versus usual clinical care or no allergy assessment. Observational studies had found that penicillin allergy assessment can increase penicillin use, but such studies were prone to bias. Risk factors for penicillin allergy assessment included female sex, increased age, lower levels of deprivation, general practice size (number of registered people 5000–19 999), and comorbidities. A range of health-care professionals have been involved in penicillin allergy assessment, including pharmacists, nurses, and doctors.

#### Added value of this study

Our findings support those of observational studies showing that a penicillin allergy assessment can increase penicillin use for infections where penicillins are the recommended first-line therapy, and have quantified the effect size. We also found that a penicillin allergy assessment pathway might reduce total antibiotic prescribing. We developed methods for improving engagement with penicillin allergy assessment and delabelling that can be applied more broadly in general practice.

#### Implications of all the available evidence

Given the considerable body of evidence linking patient harms to penicillin allergy labels—observational studies that indicate most patients with penicillin allergy labels are not actually allergic, observational studies showing that delabelling patients with incorrect penicillin allergy labels is feasible and is associated with improved antibiotic prescribing, and now a randomised trial that supports that penicillin allergy assessment cost-effectively improves antibiotic prescribing, even if done in advance of need in primary care patients—access to penicillin allergy assessment for patients should be widened. We observed prescribing benefits over a 1-year follow-up, but there might be continued benefits beyond 1 year, which needs further research. More research is also needed to evaluate the applicability of our findings to non-White individuals, to assess if there are subsets of patients with a very low risk of penicillin allergy who might be suitable for allergy assessment by their general practitioner, and to evaluate the effect on patient health outcomes.

Full details of the protocol have been published elsewhere[12] and the final working version is in the appendix (pp 4–59). Standard Protocol Items Recommendations for Interventional Trials guidelines were followed.[13] The trial was overseen by an independent data and safety monitoring board and trial steering committee. Patient and public involvement and engagement was integrated throughout trial design and delivery.[12] Participants were initially recruited into the nested pilot trial (participants who consented between Sept 17, 2019, and April 12, 2020) to assess the safety, feasibility, acceptability, and practicality of the trial. Once stop–go criteria were assessed by the independent data and safety monitoring board and trial steering committee (based on participant recruitment target), recruitment continued to the main part of the trial. The study was registered with ISRCTN on Feb 14, 2019, ISRCTN20579216, and ClinicalTrials.gov, NCT04108637, on Sept 30, 2019. The trial was sponsored by the University of Leeds, UK. Patients provided informed consent (written or orally via telephone). The trial started with the first consent on Sept 17, 2019. Random assignment of consented participants started at the first general practice site as part of the pilot study on Sept 19, 2019, and finished on Oct 9, 2023. Recruitment was paused due to the COVID-19 pandemic on April 12, 2020, and restarted on Jan 11, 2021. Trial process evaluation work (protocol section 7.9 and 11.8) has been reported elsewhere.[14,15]

UK National Research Ethics Service approval was granted by the London Bridge Committee (reference 19/LO/0176) and approved protocol amendments are in the appendix (pp 211–215). The original primary outcome was treatment response failure, but this was later revised to penicillin prescribing due to challenges in recruitment because of the COVID-19 pandemic.[12,16] Although revision of the primary outcome is typically considered undesirable, the pandemic placed many trials and funders in unprecedented situations for which remedial actions were sought. The ALABAMA primary outcome was revised in full consultation and deliberation with the National Institute for Health and Care Research (NIHR) funding panel and the trial steering committee and was operationalised before completion of recruitment. NIHR approval for the revised primary outcome was granted on May 16, 2023, and NHS research ethics committee approval was received on July 12, 2023. The choice of the revised primary outcome was deemed to be clinically important and relevant because oral penicillins are WHO Access category antibiotics that are associated with reduced resistance and considered a first-line therapy for many common infections. The revised primary outcome was actually the primary outcome originally proposed by the research team to the NIHR at the time of funding application, but they preferred a patient health outcome that required a substantially greater sample size. Infections for which penicillin was indicated as a first-line therapy were considered primary events in the original primary outcome definition and were kept the same for the revised primary outcome (appendix pp 211–215). The cost-effectiveness analysis was also modified at the request of the funder to extend beyond the 12-month endpoint and include a value of information analysis; however, the within 12-month trial analysis reported herein was unaffected by this change.

### Participants

Participants were recruited from NHS general practices in England. Potential participants were identified using a search of electronic health records at their general practice. Eligible participants were aged 18 years or older, provided informed consent, had a record of penicillin allergy or sensitivity in their electronic health records, had received an antibiotic prescription in the previous 24 months (in the previous 12 months for pilot study participants; appendix p 19), and were outpatients at the time of recruitment. Patients with a history consistent with anaphylaxis or serious cutaneous reactions caused by a penicillin were excluded from the trial by general practitioners at the point of screening according to patient history and medical notes; therefore, patients at low risk of serious reactions were recruited to the trial (appendix pp 19–20). The remaining patients were asked for consent and randomly assigned. Participants did not have previous contact with the research team. The recruitment process, participant journey through trial processes, and location of participants during different stages of the pathway are shown in the appendix (p 170). Eligibility was rechecked at baseline and any symptoms suggestive of serious reactions were reviewed using the trial suitability and risk stratification tool in the appendix (pp 60–64). Sex data were recorded from the patient primary care electronic health record during the baseline telephone call. Ethnicity data were collected from primary care records, or from secondary care records during medical notes review.

### Randomisation and masking

During a telephone call with the research team, participants were asked if they had taken any antibiotics in the previous 2 weeks; if they had, random assignment and the baseline call were postponed (in which case, the research team then arranged for another call when the participant had been free of antibiotic use for 2 weeks). During the baseline telephone call, participants were randomly assigned (1:1) to either the penicillin allergy assessment pathway or usual clinical care. Minimisation was done by a member of the research team (SA and various members of the ALABAMA trial research group) using an online validated randomisation system, Sortition (version 2.3), with the first five participants assigned using simple random assignment followed by a non-deterministic minimisation algorithm, with an allocation probability of 0·8, to ensure general practice site, age, number of antibiotic prescriptions in the 24 months before random assignment (12 months for the nested pilot participants), and number of comorbidities were balanced across the groups. General practice site was included as a minimisation factor to ensure individual practices were

For more on the **WHO AWaRe classification of antibiotics** see https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.04

balanced across allocation groups. Due to the nature of the intervention, participants and the trial team were aware of group allocation, but trial investigators and recruiting clinicians were masked to emerging results. Statisticians who did the final analysis were also masked to group allocation.

### Procedures

The penicillin allergy assessment pathway intervention was complex and designed according to UK Medical Research Council guidance,[17] and comprised: (1) allergy history, risk stratification, and testing; (2) behaviour change materials for clinicians and patients; and (3) processes for updating medical records. The allergy history and testing components of the pathway aligned with usual NHS practice but the risk stratification tool and components 2 and 3 were specific to this trial. In theory, patients in the usual clinical care group could be referred to immunology services for penicillin allergy assessment as part of usual NHS care, according to National Institute for Health and Care Excellence (NICE) guidelines (but this did not happen during the trial).[9]

Details of the electronic health record functions used to facilitate delivery of the trial have been published elsewhere and are summarised in the appendix (p 104).[18] The penicillin allergy assessment pathway was delivered by a range of staff (SA, NP, SS, and RS plus various members of the ALABAMA trial research group), including nurses, pharmacists, and doctors. A consultant immunologist was available for consultation for all participants, as required. Those in the penicillin allergy assessment pathway group were risk stratified as suitable for direct oral challenge test or skin testing with or without an oral challenge test based on criteria similar to those described previously.[19] Testing took place in a hospital clinic (either in outpatient departments or on day case units, depending on the testing site); the bespoke trial risk stratification tool is available in the appendix (pp 60–64). After risk stratification, consent to conduct the direct oral challenge test or skin testing with or without oral challenge test was sought from participants. Skin testing followed UK guidelines and involved the implicated antibiotic if known or benzylpenicillin (appendix pp 91–103).[20] Oral challenge testing after a skin test comprised a graded oral challenge with amoxicillin (appendix pp 79–90), if the index penicillin was not known, or involved the index penicillin. Direct oral challenge initially involved a graded challenge, but a single dose of 500 mg amoxicillin (appendix p 88) was introduced as an option during the trial. Graded oral challenge was used initially because this was the standard of care in Leeds Teaching Hospitals NHS Trust immunology department at the time of trial design, and this was the primary trial site. The option for a single 500 mg dose of amoxicillin was ethically approved on June 14, 2022, for participants who were risk stratified as suitable for direct oral challenge when Sheffield began to recruit patients, because this was their standard of care at the time. The standard operating procedures for oral challenge testing and skin testing are available in the appendix (pp 79–103). A prolonged oral challenge test was used in all participants, which involved a 3-day course of the antibiotic to be taken at home after the supervised oral challenge test. Development of the behavioural intervention components has been reported elsewhere.[21] Behaviour change materials included (1) an information booklet for clinicians, (2) a pre-test booklet for all participants, and (3) post-test booklets for participants that were tailored to the results, as well as pop-up alerts to general practitioners (appendix pp 65–78). When a general practitioner prescribed an antibiotic for a participant, a pop-up alert in the electronic health record system notified the practitioner that a patient had been allergy tested and the result was negative, thus the patient could receive penicillins again. Results were communicated to a participant's general practitioner by letter but, additionally, result letters were appended to a task sent to general practitioners within the electronic health record system to request them to update allergy records (ie, mark the allergy record in error).[18] Therefore, an audit trail was preserved and accessible but prescribing alerts were inactivated in the electronic prescribing system.

Baseline allergy history and clinical data were recorded at the time of random assignment. Participants allocated to the penicillin allergy assessment pathway had their penicillin allergy history and clinical information rechecked at the time of testing and were followed up by telephone on days 4–6 (after completion of the prolonged oral challenge test to enquire about any delayed reactions) and days 28–30 after completion of the oral challenge test for safety outcomes. A list of potential adverse events was provided, as well as an option for self-reported events, which aligned with the protocol (appendix pp 29–31). Potential primary outcome events were identified by active surveillance during follow-up: weekday antibiotic prescribing reports were generated in SystmOne[18] (primary care electronic health record system) to identify participants who had been prescribed antibiotics in primary care; these participants were contacted by telephone to collect outcome data at days 2–4 and 28–30 (which included antibiotics prescribed) and to remind participants to complete daily diaries detailing infection symptoms and their severity, and antibiotic consumption. Participants were asked to self-report their predominant symptoms either in a paper diary or an online version. Primary outcome events were infections for which penicillin was considered the first-line therapy.[12] Quality-adjusted life-years (QALYs) were derived from the general quality-of-life questionnaire EQ-5D-5L measure, which was recorded at baseline, 12 months, and at the time of any primary outcome events occurring between these timepoints. 12-month outcome data were collected from several sources: participant follow-up calls, case-note review, primary and secondary antibiotic prescribing reports, and Hospital Episode Statistics (HES) and Office for National Statistics (ONS) reports. Further information about antibiotic report generation in the trial in SystmOne can be found elsewhere.[18] Once participants were randomly assigned to the penicillin allergy assessment pathway, they could be seen by any general practitioner thereafter. Likewise, usual clinical

care participants could be seen by any general practitioner. Sites were remunerated per participant for taking part and trial participants were assessed separately from routine NHS referrals.

### Outcomes

The original primary outcome was treatment response failure, defined as re-presentation with worsening or non-resolving or new symptoms after treatment with an antibiotic up to 28 days after the initial antibiotic prescription (for predefined infections; appendix p 171), but this was later revised to penicillin prescribing, defined as the proportion of participants who received at least one prescription for a penicillin for predefined conditions where a penicillin is the first-line recommended therapy (appendix p 171) up to 12 months after random assignment. Secondary outcomes were treatment response failure (the original primary outcome), symptom duration, total antibiotic use (total number of prescriptions, defined daily dose [DDD], and days of therapy), penicillin use (number of prescriptions, DDD, and days of therapy), non-penicillin use (number of prescriptions, DDD, and days of therapy), admission to hospital (within 56 days of the index prescription), number of hospital admissions (within 56 days of the index prescription), length of hospital stays (within 56 days of the index prescription), mortality rates, number of participants with meticillin-resistant *Staphylococcus aureus* (MRSA) infection or colonisation, number of participants with *Clostridioides difficile* infection (CDI), and delabelling rates at 3 months and 12 months after random assignment. Symptom duration was based on the duration of symptoms rated moderately bad or worse by patients (using symptom diaries after antibiotic prescription for a primary event).[22] Antibiotic use was measured in terms of participants receiving the antibiotic, number of prescriptions, number of days of therapy, and DDD. The secondary outcomes of exploring patient and clinician views and experiences of penicillin allergy testing, test results and future antibiotic use, and experiences of trial procedures are reported elsewhere.[14,15] Analysis methods for these qualitative research outcomes are reported in the associated papers and therefore were not included in the trial statistical analysis plan. The cost-effectiveness for the intervention relative to usual care was analysed through EQ-5D-5L and cost of health-care resource use measures, as described in the Health Economic Analysis section.

### Statistical analysis

The original planned sample size was based on treatment response failure as the primary outcome.[12] The revised sample size, undertaken before the start of the analysis, was based on penicillin prescribing.[16] A total sample of 848 participants (424 per group) was required to provide 90% power to detect an increase of 10% in the proportion of penicillin prescription (from 4% [usual clinical care] to 14% [penicillin allergy assessment pathway]) during the year after random assignment, at a 5% level of statistical significance (two-sided) and 10% attrition. A recruitment target of 96 participants was set for the pilot phase. Trial stop–go criteria were set by the independent data and safety monitoring board and trial steering committee as 80% recruitment to the pilot phase and no patient safety concerns, to indicate if progression to the main trial should proceed. The sample size was calculated assuming 50% of participants would require at least one prescription within 12 months of random assignment. The sample size did not account for any clustering effect within general practices.

Planned analyses are described in detail in the statistical analysis plan (appendix pp 105–140), which was finalised before the analysis. The primary analysis population was defined as all participants for whom outcome data were available and was analysed according to the groups they were randomly allocated to, regardless of deviation from the protocol. This population included all randomly assigned participants who had partial follow-up periods; missing data were not imputed and participants found to be ineligible after random assignment were excluded. The prespecified analysis for the primary outcome, penicillin prescribing within 12 months of random assignment, used a binomial mixed-effects generalised linear model with a logit link function fitted. The model included allocated group, age, number of antibiotic prescriptions up to 24 months before random assignment, and number of comorbidities at baseline as fixed effects. General practitioner site was included as a random effect. The adjusted marginal relative risk and corresponding risk difference between the allocated groups and the corresponding 95% CIs were obtained from the model using delta-method SEs and reported alongside the associated p value. A similar approach was used for other binary secondary outcomes. For outcomes where the number of events was so small that the models would not converge, unadjusted analyses were done. Continuous outcomes were analysed using linear mixed-effects models and non-parametric methods, such as quantile regression, adjusting for the same fixed effects as the primary outcome analysis if assumptions underlying these models were violated. For the continuous outcomes of number of days of antibiotic use and defined daily doses, we prespecified analyses by total antibiotic use, followed by separate analyses by penicillin and non-penicillin class antibiotics. Count outcomes were analysed using Poisson mixed-effects regression models, adjusted for fixed and random effects, as was done for the primary outcome analysis. We had no plan to adjust for multiple comparisons. Missing data were reported for all analyses, with reasons where available. The safety analysis was carried out in the as-treated population—that is, participants were analysed by the intervention they received. The number and proportion of participants with at least one serious adverse event was reported by the intervention they received (rather than the intervention they were randomly assigned to receive) and was analysed with Fisher's exact test, where possible. There were no interim analyses. The primary analysis population was used for analysis of the primary outcome and all

secondary outcomes, except the delabelling outcomes, for which the as-treated population was used.

Four sensitivity analyses were prespecified in the statistical analysis plan. In the first sensitivity analysis, participants were analysed based on which intervention they received; participants who were allocated to the penicillin allergy assessment pathway and completed either the skin test or oral challenge test or both were included in the as-treated penicillin allergy assessment pathway group. Those who were allocated to the penicillin allergy assessment pathway but did not have the test and those who were allocated to usual clinical care were included in the usual clinical care group. The second sensitivity analysis was to explore the association between baseline characteristics and the availability of the primary outcome; because no participants were missing a primary outcome, this analysis was not done. The third sensitivity analysis was to assess the effect of shortened follow-up on the primary outcome. Participants recruited after March 5, 2023, were not followed up for the full 12 months of the planned follow-up period due to the end of the study. A sensitivity analysis was done to rerun the primary analysis with these 135 participants excluded and the fourth sensitivity analysis was to establish the effect of a delayed penicillin allergy assessment pathway on the primary outcome. The primary analysis was rerun excluding participants who were delayed in receiving the penicillin allergy assessment pathway test by more than 3 months (90 days) after random assignment. Three subgroup analyses were prespecified in the statistical analysis plan: age (<65 years *vs* ≥65 years), number of Quality and Outcomes Framework-registered conditions at baseline (less than two *vs* two or more), and index of multiple deprivation (split at the median). All analyses were done in Stata SE version 18.

### Health economic analysis

When the primary outcome was changed, there were also changes to the protocol to expand the cost-effectiveness analysis.[16] Other substantial amendments are listed in the appendix (pp 50–58). We estimated the incremental cost per QALYs gained by undergoing a penicillin allergy assessment pathway following the NICE reference case. We estimated costs of the penicillin allergy assessment pathway intervention according to the type of test done for each trial participant (ie, skin test with or without oral challenge test or direct oral challenge test). We used individual participant data collected during the trial, including primary electronic health record data for general practitioner and nurse consultations and antibiotic prescriptions; HES for inpatient admissions, outpatient attendance, and emergency department attendance data; and ONS data for civic registrations of death. Individual participant data were analysed using a mixed-effects model for costs and QALYs, controlling for baseline minimisation factors and random effects for general practice (appendix pp 196–197) and using multiple imputation of missing data. We estimated incremental cost-effectiveness ratios (ICERs) and net benefit measures at willingness-to-pay values of £20 000 per QALY. Cost figures are presented in £ at 2022–23 prices. We investigated the robustness of results to changing the cost of the penicillin allergy assessment pathway, excluding any health-care resource use after 56 days of an index antibiotic prescription and varying methods, including adjustment for censoring in sensitivity analyses. Subgroup analyses are presented by age (<65 years *vs* ≥65 years), sex (female *vs* male), number of quality and outcomes framework conditions (<2 *vs* ≥2), and number of antibiotic prescriptions at baseline. Full details are presented in the appendix (pp 187–203).

For more on the **NICE reference case** see https://www.nice.org.uk/process/pmg9/chapter/the-reference-case

### Role of the funding source

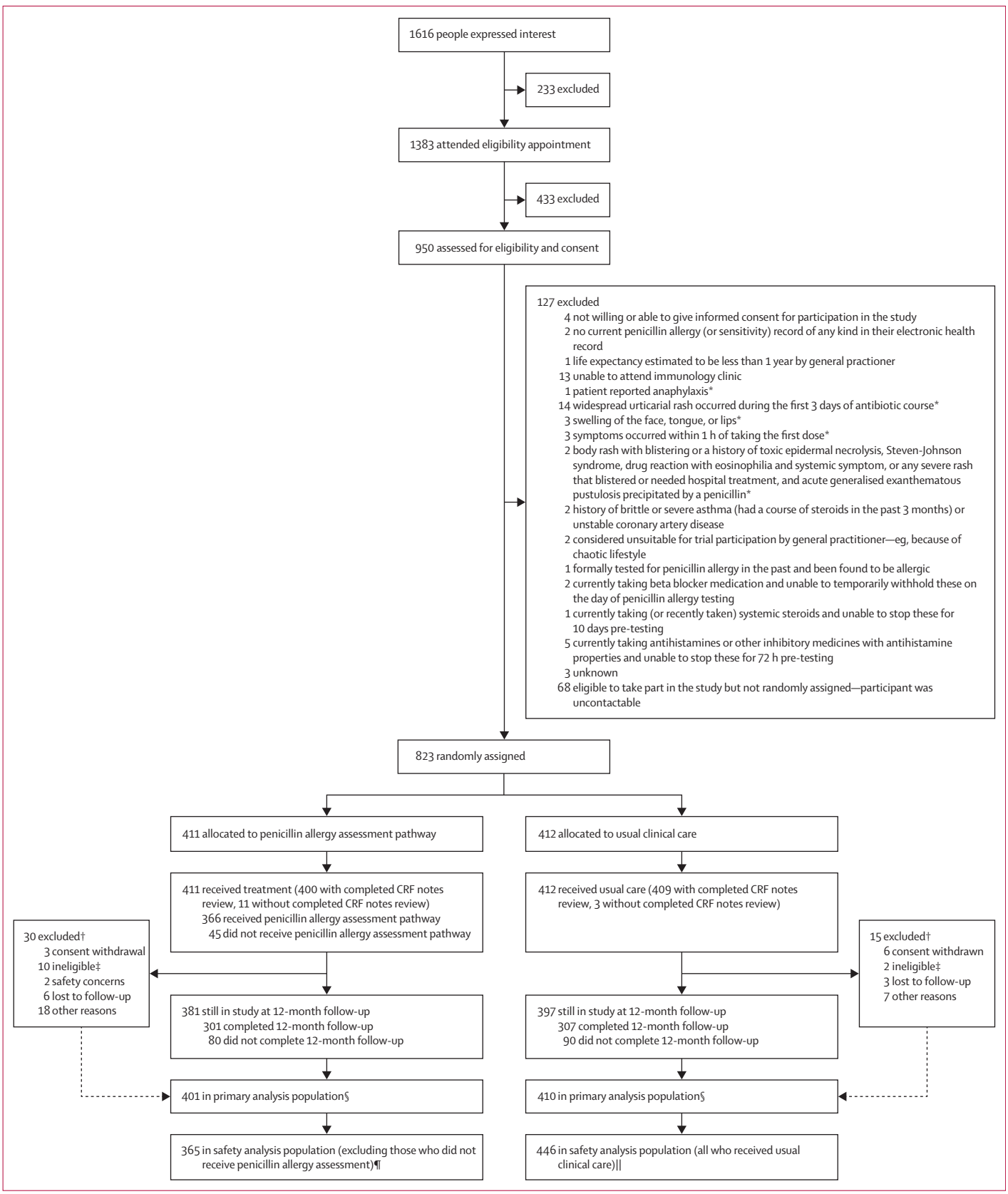
The funder of the study had no role in data collection, data analysis, data interpretation, or writing of the report. The funder approved the original study design and change to primary outcome.

## Results

During the nested pilot study, 81 participants consented and were randomly assigned. At the stop–go assessment, the independent data and safety monitoring board and trial steering committee found the study to be safe and feasible, and recruitment had reached the prespecified criteria for progression, so approval was given to progress to the main trial.

Between Sept 17, 2019, and Oct 9, 2023, 1616 participants expressed interest and 823 were enrolled and randomly allocated (411 to the penicillin allergy assessment pathway and 412 to usual clinical care; figure). There were a median 15 participants per general practice (IQR 8·0 to 26·5). The primary analysis included 811 participants (401 in the penicillin allergy assessment pathway and 410 in usual clinical care); 12 patients who appeared to be eligible at baseline assessment were subsequently found not to be and were excluded from the analysis. Baseline characteristics were similar between the two groups (table 1). 584 (72%) of 811 patients were female and 227 (28%) were male. The mean participant age was 55 years (SD 15·6). 786 (97%) of 811 participants were White and 13 (2%) were non-White. Details of patient-reported allergy history at baseline are shown in the appendix (pp 172–173), as are minimisation factors (appendix p 174); a data availability summary by assessment point (p 174); and details of completion of follow-up assessments, withdrawals, and participants lost to follow-up (p 175).

72 (18%) of 411 participants in the penicillin allergy assessment pathway group and 14 (3%) of 412 participants in the usual clinical care group were prescribed at least one course of a penicillin during follow-up. We found evidence that the penicillin allergy assessment pathway significantly increased prescribing of penicillins (adjusted relative risk 5·27, 95% CI 3·03 to 9·18; adjusted risk difference 14·21%, 9·92 to 18·49; table 2). Results of sensitivity analyses excluding participants who were delayed in receiving the intervention or who did not have complete follow-up, and


1616 people expressed interest
233 excluded
1383 attended eligibility appointment
433 excluded
950 assessed for eligibility and consent
127 excluded
4 not willing or able to give informed consent for participation in the study
2 no current penicillin allergy (or sensitivity) record of any kind in their electronic health record
1 life expectancy estimated to be less than 1 year by general practioner
13 unable to attend immunology clinic
1 patient reported anaphylaxis*
14 widespread urticarial rash occurred during the first 3 days of antibiotic course*
3 swelling of the face, tongue, or lips*
3 symptoms occurred within 1 h of taking the first dose*
2 body rash with blistering or a history of toxic epidermal necrolysis, Steven-Johnson syndrome, drug reaction with eosinophilia and systemic symptom, or any severe rash that blistered or needed hospital treatment, and acute generalised exanthematous pustulosis precipitated by a penicillin*
2 history of brittle or severe asthma (had a course of steroids in the past 3 months) or unstable coronary artery disease
2 considered unsuitable for trial participation by general practitioner—eg, because of chaotic lifestyle
1 formally tested for penicillin allergy in the past and been found to be allergic
2 currently taking beta blocker medication and unable to temporarily withhold these on the day of penicillin allergy testing
1 currently taking (or recently taken) systemic steroids and unable to stop these for 10 days pre-testing
5 currently taking antihistamines or other inhibitory medicines with antihistamine properties and unable to stop these for 72 h pre-testing
3 unknown
68 eligible to take part in the study but not randomly assigned—participant was uncontactable
823 randomly assigned
411 allocated to penicillin allergy assessment pathway
412 allocated to usual clinical care
411 received treatment (400 with completed CRF notes review, 11 without completed CRF notes review)
366 received penicillin allergy assessment pathway
45 did not receive penicillin allergy assessment pathway
412 received usual care (409 with completed CRF notes review, 3 without completed CRF notes review)
30 excluded†
3 consent withdrawal
10 ineligible‡
2 safety concerns
6 lost to follow-up
18 other reasons
15 excluded†
6 consent withdrawn
2 ineligible‡
3 lost to follow-up
7 other reasons
381 still in study at 12-month follow-up
301 completed 12-month follow-up
80 did not complete 12-month follow-up
397 still in study at 12-month follow-up
307 completed 12-month follow-up
90 did not complete 12-month follow-up
401 in primary analysis population§
410 in primary analysis population§
365 in safety analysis population (excluding those who did not receive penicillin allergy assessment)¶
446 in safety analysis population (all who received usual clinical care)||

analysing the as-treated population, did not alter the findings (appendix p 181). Planned subgroup analyses did not show a significant interaction effect between allocation group and age, number of comorbidities, or deprivation score (appendix p 182). The penicillins prescribed to participants in the penicillin allergy assessment pathway group are shown in the appendix (pp 183–184). 45 participants allocated to the penicillin allergy assessment pathway did not receive the planned intervention and received usual clinical care (figure).

In the primary analysis population, 365 (91%) of 401 participants allocated to the penicillin allergy assessment pathway were tested. 234 (64%) of 365 participants had a direct oral challenge test (13 tested positive), 131 (36%) had skin testing (three tested positive), and 128 (35%) had an oral challenge test after skin testing (14 tested positive). 30 (8%) of 365 participants tested positive (on either skin testing or oral challenge test) and 335 (92%) tested negative. At 3 months after random assignment, 276 (76%) of 365 participants in the penicillin allergy assessment pathway group were delabelled, and at 12 months from random assignment, 321 (88%) participants in the penicillin allergy assessment pathway group were delabelled (table 3). 321 (96%) of 335 participants who tested negative were delabelled at 12 months. None of the 30 participants who tested positive were delabelled at 12 months. No participants in the usual clinical care group had a formal allergy assessment, but two (<1%) of 446 participants were delabelled by 12 months (ie, the patient's general practitioner directly delabelled these patients without any specialist consultation).

Select secondary outcomes are shown in table 2. We found no difference in the number of participants who received an antibiotic prescription, but there was a reduction in total antibiotic prescribing in the penicillin allergy assessment pathway group in terms of median DDD and number of prescriptions (table 2). Prescribing outcomes stratified by penicillin and non-penicillin antibiotics are shown in table 2. Prescribing of each different antibiotic class is shown in the appendix (p 183). Non-antibiotic prescribing secondary outcomes are shown in table 2, and exploratory analyses of hospitalisations are shown in the appendix (p 185). There were no significant differences in treatment response failure rates, duration of symptoms rated moderately bad or worse, number of hospital admissions, length of hospital stay, or mortality between groups. MRSA and CDI rates were so low that formal comparison was not done.

We found no significant differences in serious adverse event rates between the trial groups. 27 (7%) of 365 participants who received the penicillin allergy assessment pathway and 34 (8%) of 446 participants who received usual clinical care had at least one serious adverse event during the 1-year follow-up. 83 adverse events occurred in 73 participants in the 28 days after allergy testing; one event of gastro-oesophageal reflux was categorised as severe and was probably related to the intervention. Details of adverse events and adverse reactions from the test are shown in table 2 and the appendix (pp 185–186).

Detailed results of the economic evaluation are provided in the appendix (pp 191–203). The mean per patient costs of the penicillin allergy assessment pathway were £170 in the intervention group (401 participants; trial primary analysis population; appendix p 198). At 12 months, mean cost differences in the penicillin allergy assessment pathway relative to usual clinical care were –£10·82 (95% CI –24·33 to 2·69) for primary care, –£113·67 (–431·58 to 204·23) for hospital admissions, £0·17 (–99·65 to 99·98) for outpatient attendances, and –£12·88 (–42·29 to 16·53) for emergency care (appendix p 199). Similar figures were obtained after adjusting for baseline minimisation factors and random effects of general practice, which resulted in an incremental cost of the penicillin allergy assessment pathway of £33·93 (–416·05 to 483·91) per patient (table 4). The imputed analysis (811 participants) showed that the penicillin allergy assessment pathway was associated with an ICER of £10 938 per QALY gained relative to usual clinical care and had a 57·85% probability of being cost-effective at the £20 000 willingness-to-pay threshold (appendix p 202). In sensitivity analyses, the ICER point estimates for 56-day costing and Leeds costing were below £20 000 and resulted in a probability of cost-effectiveness greater than 50%; in the as-treated analysis and the analysis with penicillin allergy assessment pathway costs at the day case allergy visit tariff, ICER point estimates were £46 584 and £45 873, respectively (appendix p 202). Subgroup analyses of cost-effectiveness and other analyses are presented in the appendix (appendix p 203). Other results are presented in the appendix (pp 188–207).

## Discussion

Our data suggest that the penicillin allergy assessment pathway could lead to a significant increase in penicillin prescribing, while reducing overall antibiotic use (total DDD and total number of prescriptions), producing sustained delabelling, and being cost-effective. Most participants followed their randomly assigned treatment strategy and trial retention was high, indicating that the trial design and interventions were acceptable.

It is common for a subset of patients who test negative on allergy assessment to keep their penicillin allergy label. In examples from the UK and the USA, only 85% and 89% of patients who tested negative on allergy assessment were

***Figure:*** **Trial profile**

CRF refers to the form that captured the review of the participants' primary and secondary care medical notes. Safety analysis includes the as-treated population. CRF=case report form. *In relation to previous penicillin courses. †Not mutually exclusive. ‡Participants found to be ineligible after random assignment and excluded from the primary analysis population. §Excluding the ineligible patients. ¶Excluding those who did not receive penicillin allergy assessment and one of the ten ineligible patients. ||412 allocated to usual clinical care plus 45 who were allocated to the penicillin allergy assessment pathway who did not receive it, minus the 11 ineligible patients, nine of whom came from the penicillin allergy assessment pathway group.

delabelled in their medical records, respectively.[23,24] This is a failure of the penicillin allergy assessment pathway and was why we went to such lengths to incorporate delabelling processes into our trial pathway (and why it was important to assess the pathway in its entirety, not just the results of testing). 96% of the subset of participants in our trial who tested negative were delabelled, indicating an improved but imperfect delabelling process that requires further development.

Antimicrobial stewardship guidance from the Infectious Diseases Society of America[25] and WHO[26] encourages penicillin allergy evaluation but does not consider it to have a strong evidence base given the lack of adequately powered randomised trials evaluating penicillin allergy assessment versus usual clinical care or no penicillin allergy assessment. Therefore, implementation of penicillin allergy delabelling has been slow to spread beyond allergy specialists. In the absence of previous adequately powered randomised trials, it has not been possible to accurately establish the effect of penicillin allergy assessment on penicillin prescribing. Using propensity-score matching in a single-centre study of penicillin allergy assessment in Australia, investigators found there was a 9-times increase in penicillin use in those who were delabelled versus control participants (odds ratio 9·02, 95% CI 5·23 to 15·56).[27] A US retrospective age-matched and sex-matched comparison found an 18-times increase in the proportion of patients receiving a penicillin in those who had been allergy tested versus control subjects with a penicillin allergy record who had not been tested,[28] and an 80-patient pilot randomised trial of direct challenge testing with a penicillin reported that the odds ratio for receiving a penicillin after random assignment was 4·33 (95% CI 1·27 to 14·78; p=0·019).[29] Observational studies have found much larger increases in penicillin use than in our study but in a different healthcare context, as our participants were well at the time of recruitment per general practitioner assessment.[27,28] Our trial findings are important in the context of the global threat of antibiotic resistance, because this is a novel approach to reducing antibiotic prescribing in primary care. The ALABAMA trial indicates that a penicillin allergy assessment pathway has the potential to reduce the overall number of antibiotic prescriptions and antibiotic DDD and could therefore contribute to a reduction in antimicrobial resistance. In line with previous large primary care database studies in England,[3,30] in the participants assigned to usual clinical care, a higher proportion were prescribed macrolides, tetracyclines, and cephalosporins compared with participants without a penicillin allergy label. In contrast to previous studies, there was no fluoroquinolone prescribing in our study. That the number of participants who received at least one prescription for an antibiotic between the trial groups was not significantly different indicates that there was no apparent discrepancy in susceptibility to infection among participants. We would expect participants to be balanced in terms of susceptibility to infection and would therefore expect similar proportions of people in each group

| | Penicillin allergy assessment pathway group (n=401) | Usual clinical care group (n=410) |
|---|---|---|
| Age, years | 54·9 (15·9) | 55·2 (15·3) |
| Sex | | |
| Male | 109 (27%) | 118 (29%) |
| Female | 292 (73%) | 292 (71%) |
| Ethnicity*† | | |
| White | 387 (97%) | 399 (97%) |
| Mixed or Multiple ethnic groups | 3 (1%) | 2 (<1%) |
| Asian or Asian British | 3 (1%) | 3 (1%) |
| Black, African, Caribbean or Black British | 1 (<1%) | 1 (<1%) |
| Missing | 7 (2%) | 5 (1%) |
| Index of Multiple Deprivation Quintile | | |
| 1 (most deprived) | 48 (12%) | 43 (10%) |
| 2 | 46 (11%) | 54 (13%) |
| 3 | 102 (25%) | 96 (23%) |
| 4 | 114 (28%) | 125 (30%) |
| 5 (least deprived) | 88 (22%) | 90 (22%) |
| Missing | 3 (1%) | 2 (<1%) |
| Any comorbidity | 324 (81%) | 330 (80%) |
| EQ-5D index value | 0·9 (0·2) | 0·9 (0·2) |
| EQ-5D visual analogue scale score | 80·4 (15·0) | 79·2 (16·4) |
| Comorbidities | | |
| Asthma | 51 (13%) | 69 (17%) |
| Atrial fibrillation | 6 (1%) | 13 (3%) |
| Blood pressure check‡ | 250 (62%) | 258 (63%) |
| Cancer | 42 (10%) | 24 (6%) |
| Coronary heart diease | 18 (4%) | 17 (4%) |
| Chronic kidney disease | 17 (4%) | 16 (4%) |
| Chronic obstructive pulmonary disease | 12 (3%) | 9 (2%) |
| Dementia | 0 | 1 (<1%) |
| Depression | 69 (17%) | 69 (17%) |
| Diabetes | 30 (7%) | 28 (7%) |
| Epilepsy | 5 (1%) | 4 (1%) |
| Heart failure | 4 (1%) | 4 (1%) |
| Hypertension | 89 (22%) | 94 (23%) |
| Learning disabilities | 0 | 0 |
| Mental health§ | 2 (<1%) | 2 (<1%) |
| Obesity | 60 (15%) | 80 (20%) |
| Osteoporosis | 6 (1%) | 1 (<1%) |
| Peripheral arterial disease | 1 (<1%) | 2 (<1%) |
| Palliative care | 3 (1%) | 0 |
| Rheumatoid arthritis | 1 (<1%) | 7 (2%) |
| Smoking | 19 (5%) | 22 (5%) |
| Stroke | 8 (2%) | 11 (3%) |
| Testing site | | |
| Leeds | 301 (75%) | 304 (74%) |
| Leeds or Bradford¶ | 58 (14%) | 58 (14%) |
| Sheffield | 25 (6%) | 30 (7%) |
| Truro (Cornwall) | 17 (4%) | 18 (4%) |

Data are mean (SD) or n (%). *Collected from medical notes review. †White includes British, Irish, Gypsy or Irish Traveller, and any other White background. Mixed or multiple ethnic groups includes White and Black Caribbean, White and Black African, White and Asian, and any other Mixed or Multiple ethnic background. Asian or Asian British includes Indian, Pakistani, Bangladeshi, Chinese, other Asian background, and Asian British. Black, African, Caribbean, or Black British includes other Black, African, or Caribbean background. ‡Had their blood pressure checked at general practice (used as a general measure of participant–general practitioner interaction across groups). §Serious mental illness as required for Quality and Outcome Framework registration. ¶It was not possible to separate patients recruited by Bradford general practitioners by testing site, as some chose Leeds and some chose Bradford.

***Table 1:*** **Baseline characteristics in the primary analysis population**

| | Penicillin allergy assessment pathway | Usual clinical care | Treatment effect (95% CI)* | p value |
|---|---|---|---|---|
| **Primary outcome** | | | | |
| Received a penicillin prescription(s) when attending for predefined conditions where a penicillin is the first-line recommended antibiotic therapy | 72/401 (18%) | 14/410 (3%) | 5·27 [3·03 to 9·18]‖; 14·21% (9·92 to 18·49)† | <0·0001 |
| **Secondary outcomes** | | | | |
| Total antibiotic use | | | | |
| Received a prescription for an antibiotic | 163/401 (41%) | 183/410 (45%) | 0·90 (0·77 to 1·05)‡ | 0·20 |
| Number of prescriptions for all antibiotics | 2·3 (1·8) [163] | 2·7 (2·6) [183] | 0·83 (0·72 to 0·95)§ | 0·0094 |
| Number of days of therapy | 12·0 (8·0 to 22·0) [163] | 14 (8 to 26) [183] | –0·86 (–5·30 to 3·58)¶ | 0·70 |
| Defined daily doses | 6·0 (2·0 to 14·0) [163] | 8·0 (5·6 to 22·0) [182] | –3·17 (–6·11 to –0·23)¶ | 0·035 |
| Penicillin use | | | | |
| Received a prescription for a penicillin | 91/401 (23%) | 18/410 (4%) | 5·17 (3·19 to 8·39)‖ | <0·0001 |
| Number of prescriptions for a penicillin | 1·6 (1·1) [91] | 1·3 (0·8) [18] | 1·29 (0·82 to 2·02)** | 0·27 |
| Total number of days of prescriptions for a penicillin | 8·0 (6·0 to 14·0) [91] | 7·0 (6·0 to 11·0) [18] | 0·00 (–4·96 to 4·96)†† | >0·99 |
| Total defined daily dose for all prescriptions of a penicillin | 2·5 (2·0 to 4·2) [91] | 2·0 (1·7 to 2·7) [17] | 0·41 (–0·81 to 1·63)†† | 0·51 |
| Non-penicillin use | | | | |
| Received a prescription for non-penicillin antibiotics | 112/401 (28%) | 174/410 (42%) | 0·65 (0·54 to 0·79)‡ | <0·0001 |
| Number of prescriptions for non-penicillin antibiotics | 2·0 (1·4) [112] | 2·7 (2·5) [174] | 0·72 (0·61 to 0·84)§ | 0·0001 |
| Total number of days of prescriptions for non-penicillin antibiotics | 9·0 (8·0 to 18·5) [112] | 14·0 (8·0 to 28·0) [174] | –2·29 (–6·52 to 1·93)¶ | 0·29 |
| Total defined daily dose for prescriptions of non-penicillin antibiotics | 8·0 (5·0 to 16·0) [110] | 8·8 (6·0 to 22·0) [174] | –2·47 (–5·21 to 0·27)¶ | 0·076 |
| **Non-prescribing secondary outcomes** | | | | |
| Treatment response failure | 125/401 (31%) | 133/410 (32%) | 0·96 (0·79 to 1·17)‡ | 0·67 |
| Duration of symptoms rated moderately bad or worse, days | 5·0 (2·0 to 8·0) [113] | 4·0 (3·0 to 7·0) [116] | 0·33 (–0·89 to 1·56)¶ | 0·59 |
| Admitted to hospital within 56 days of the index prescription | 7/401 (2%) | 9/410 (2%) | 0·82 (0·31 to 2·14)‡ | 0·68 |
| Number of hospital admissions within 56 days of the index prescription | 1·3 (0·8) [7] | 1·1 (0·3) [9] | 1·16 (0·47 to 2·87)§ | 0·75 |
| Length of hospital stay for admissions within 56 days of the index prescription, days | 2·0 (1·0 to 6·0) [7] | 3·0 (2·0 to 6·0) [9] | –0·73 (–4·54 to 3·07)¶ | 0·68 |
| Mortality | 3/401 (1%) | 3/410 (1%) | 1·02 (0·21 to 5·04) | 0·98 |
| Meticillin-resistant *Staphylococcus aureus* infection or colonisation | 1/395 (<1%) | 2/407 (<1%) | .. | >0·99‡‡ |
| *Clostridioides difficile* infection | 0/394 | 1/407 (<1%) | .. | >0·99‡‡ |
| **Safety outcomes (as-treated population)** | | | | |
| Number of participants with at least one adverse event within 3 days of the penicillin allergy assessment pathway test | 73/365 (20%) | 0/446 | 20·0% (15·9 to 24·1) | <0·0001 |
| Number of participants with at least one serious adverse event during the trial period | 27/365 (7%) | 34/446 (8%) | –0·23% (–3·87 to 3·42) | >0·99 |

Data are n/N(%), mean (SD) [n], or median (IQR) [n]. *Penicillin allergy assessment pathway versus usual clinical care. †A risk difference >0 indicates improvement in favour of the penicillin allergy assessment pathway. ‡A relative risk <1 indicates improvement in favour of penicillin allergy assessment pathway. §An incidence rate ratio <1 indicates improvement in favour of the penicillin allergy assessment pathway. ¶A negative value of median difference indicates improvement in favour of the penicillin allergy assessment pathway. ‖A relative risk >1 indicates improvement in favour of the penicillin allergy assessment pathway. **An incidence rate ratio >1 indicates improvement in favour of the penicillin allergy assessment pathway. ††A positive value of median difference indicates improvement in favour of the penicillin allergy assessment pathway. ‡‡Fisher's exact test.

***Table 2:*** **Primary, select secondary, and safety outcomes**

to present with symptoms suspected to be infections warranting antibiotic treatment. A significant difference between the number of prescriptions for any antibiotic between the penicillin allergy assessment pathway and usual clinical care groups, with more prescriptions in the usual clinical care group, suggests that these individuals required more treatment courses, which might imply there were more treatment failures with, or intolerance of, non-penicillins. Further study with a larger sample size is warranted to examine this finding further. Participants in the penicillin allergy assessment pathway group had significantly more penicillin prescriptions than those in the usual clinical care group, but the number of days of therapy with a penicillin and penicillin DDDs were not significantly different between groups, indicating consistency in course length and dosing when a penicillin was chosen. Significantly fewer participants in the penicillin allergy assessment pathway group received non-penicillin antibiotic prescriptions than in the usual clinical care group and there were significantly fewer prescriptions of a non-penicillin in the penicillin allergy assessment pathway group. Among those treated with a non-penicillin antibiotic, days of treatment and DDDs were not significantly different between the treatment groups, indicating consistency of

dose and duration when prescribed. Although allowing more participants to be treated with first-line therapy might be expected to improve participant outcomes, we found no effect on duration of symptoms or treatment response failure; however, the trial was underpowered to detect a difference compared with the original planned sample size.[12] Further randomised trials and meta-analyses are required to examine this finding. Numbers of participants with MRSA and CDI were too small to analyse, which is unsurprising as big-data studies have been needed to detect an increased risk of these infections.[3,30]

Although systematic reviews have indicated that penicillin allergy assessment is associated with changes to antibiotic prescribing and is safe and feasible, including for patients at low risk of a serious immune-mediated reaction who were assessed by non-specialists,[11] most studies have been observational, uncontrolled evaluations that are subject to a high risk of bias. We recruited people at low risk of serious reactions based on allergy history, many of whom were suitable for direct oral challenge test, making testing at scale feasible.

Our study has several limitations. General practitioners involved in the trial received intervention materials that might have affected their behaviour across all participants, for example, the materials gave information about the frequency of incorrect penicillin allergy records and the associated harms, and might have lowered practitioners' threshold for removing penicillin allergy records where the history was not suggestive of a true allergy (appendix pp 66–67). However, we found little objective evidence of this as only two participants in the usual clinical care group were delabelled by their general practitioner. In addition, rates of penicillin prescribing to participants in the usual clinical care group were similar to those seen in a large population-based analysis of English patients with a penicillin allergy label in general practice.[3] In terms of generalisability, participants were recruited from a range of socioeconomic backgrounds, but participant ethnicity was predominantly White. Therefore, our trial findings might not apply to people from non-White ethnicities. Causal attribution of serious adverse events related to penicillin allergy testing was determined by the research team and might have been liable to potential biases of unknown effect. We excluded patients with a history consistent with anaphylaxis because there were concerns about the safety of including such patients at the time of trial design; therefore, our potential pool of people who could have been delabelled was reduced.

This trial was affected by the COVID-19 pandemic, which slowed recruitment and testing capacity. The pandemic delayed random assignment for some participants and interrupted follow-up. Due to slower recruitment than expected, funding constraints led to the primary outcome being changed and the sample size reduced.[16] The pilot trial recruitment period included the early stages of the COVID-19 pandemic, which was a period when antibiotic prescribing in the UK primary care system was reduced,[31] and therefore potentially reduced the power of the trial. The first-choice treatment for community-acquired pneumonia in the pre-COVID-19 NICE guideline was amoxicillin and second-line agents were doxycycline or macrolides.[32] From March to May, 2020, amoxicillin prescribing decreased, whereas doxycycline use increased slightly,[31] coincident with the publication of COVID-19 rapid guideline NG165,[33] which recommended doxycycline use over amoxicillin. Although we used multiple sources to capture antibiotic prescribing details, not all prescriptions will have been captured (eg, prescriptions from dentists and private hospitals).

Uncertainties remain about the optimal methods for risk assessing and testing patients with a penicillin allergy. Consistent with existing UK penicillin allergy testing guidelines, we used standard skin testing followed by oral challenge test for some participants and direct oral challenge test for others. We used a 3-day prolonged oral challenge test, which might be counterproductive to antimicrobial stewardship aims, but there is a lack of consensus about the need for and duration of prolonged oral challenge testing in penicillin allergy assessment. Use of follow-on therapy is supported by a 2024 meta-analysis of predominantly allergy-clinic studies, in which more than 50% of all hypersensitivity reactions occurred during or after extended challenges.[34] ALABAMA was novel in terms of proactively recruiting participants in primary care, in advance of need. The trial population was relatively young and in reasonably

| | Penicillin allergy assessment pathway (n=365) | Usual clinical care (n=446) | Risk difference (95% CI) | p value |
|---|---|---|---|---|
| Delabelled at 3 months after random assignment | 276 (76%) | 0 | Undefined | <0·0001 |
| Missing* | 0 | 22 (5%) | .. | .. |
| Delabelled at 12 months after random assignment | 321 (88%) | 2 (<1%) | 87·4% (84·1 to 90·9) | <0·0001 |
| Missing* | 0 | 22 (5%) | .. | .. |

*22 participants withdrew from the study before 12 months, hence missing data.

***Table 3:*** **Results of penicillin allergy delabelling (as-treated population)**

| | Mean difference (95% CI) |
|---|---|
| Intervention | £164·69 (157·72 to 171·66) |
| Primary care | £–8·59 (–21·39 to 4·21) |
| Inpatient | £–99·09 (–405·19 to 207·02) |
| Outpatient | £–8·98 (–104·79 to 86·84) |
| Emergency care | £–14·11 (–42·40 to 14·18) |
| All secondary care | £–121·98 (–552·20 to 308·23) |
| All primary or secondary care | £–130·57 (–573·59 to 312·44) |
| Total | £33·93 (–416·05 to 483·91) |

Penicillin allergy assessment pathway versus usual clinical care. Mean differences are treatment coefficient estimates derived from mixed-effects adjusted regression models. Confidence intervals were obtained using the percentile bootstrap method.

***Table 4:*** **Per-patient cost differences in pounds sterling of penicillin allergy assessment pathway versus usual care (complete-case analysis, n=612)**

good health, with relatively few admissions to hospital during follow-up, yet antibiotic prescribing benefits were seen. The benefits of a penicillin allergy assessment pathway might be greater in people with an increased risk of hospitalisation. Health-related quality-of-life outcomes for trial participants were collected at baseline and at the trial end, which for many patients was less than 12 months due to early trial termination. We used a general quality-of-life questionnaire (EQ-5D-5L) rather than a drug allergy-specific questionnaire. We used reports generated from primary care electronic health records for final 12-month antibiotic data, which we anticipate gave a high degree of accuracy, but we have not validated this. This method of data collection would have missed antibiotic prescriptions from private health-care providers and dentists, but we have no reason to believe that these limitations would not be similar across the groups and could only have contributed to underestimates of efficacy.

Our cost-effectiveness analysis reflected the English NHS perspective. Although results might vary across countries due to differences in costs and cost-effectiveness policy thresholds, the observed tendency towards reducing consultations, days in hospital, and emergency admissions is generalisable and suggest that the penicillin allergy assessment pathway is cost-effective in the short run and increasingly likely to be so over longer follow-up periods.

To our knowledge, this is the first randomised trial of a penicillin allergy assessment pathway versus usual clinical care in adult outpatients in primary care with a recent antibiotic prescription. The penicillin allergy assessment pathway increased the opportunity for patients to receive first-line treatment and is a potentially effective antimicrobial stewardship tool in primary care. Larger trials and longer-term follow-up of participants will be needed to establish whether a penicillin allergy assessment pathway improves patient health outcomes.

**ALABAMA Trial Research Group**
Emily Bongard, Kate Corfield, Mina Davoudianfar, Razan Saman, Tommaso Malavenda, Louise Savic, Alison Haigh, Emma Carter, Sammiya Ahmed, Robert White, Gary Lamont, Honorine Jobain, Claire Forrest, Samuel Skuse, Caity Roleston, Joy Rahman.

**Contributors**
Conceptualisation: JATS and SHP. Data curation: JF, RM-M, JATS, RMW, L-MY, ST-C, MW, and MS. Formal analysis: UG, SM, ST-C, MW, MS, RB, MY, RM-M, and DH. Funding acquisition: JATS, SHP, L-MY, ST-C, CCB, PH, SS, and JC. Investigation: SA, JF, NP, MS, MW, and JATS. Methodology: JATS, JB, CCB, PH, RM-M, CEP, SS, ST-C, MW, RMW, L-MY, and SHP. Project administration: CEP, KA, JF, ST-C, and RM-M. Resources: CB and SS. Software: CB, JF, JATS, and CEP. Supervision: JATS, SA, RM-M, CEP, KA, SS, ST-C, MW, L-MY, SHP, CCB, JC, and AN. Directly accessed and validated data: UG, L-MY, SM, S-TC, and RM-M. Visualisation: UG, SM, RB, MY, RM-M, and DH. Writing—original draft: JATS, RM-M, SA, SHP, and L-MY. Writing reviewing and editing: all authors. Other contributions—patient and public involvement and engagement: JB. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**Declaration of interests**
JATS is a member of the British Society for Allergy and Clinical Immunology Penicillin Allergy working party, is a panel member of the European Society for Clinical Microbiology and Infectious Diseases guideline for antibiotic allergy, was co-lead for the British Society for Antimicrobial Chemotherapy massive open access online penicillin allergy course, and has received research funding from the Engineering and Physical Sciences Council, National Institute for Health and Care Research, Welcome Trust, and Medical Research Council. SA is completing a National Institute for Health and Care Research (NIHR)-funded doctoral fellowship. CCB has received an NIHR senior investigator award. RM-M has received funding from the Leeds NIHR Biomedical Research Centre and research funding from the NIHR for the Spurious Penicillin Allergy in Secondary Care (SPACE) study. NP is completing an NIHR-funded doctoral fellowship, is a member of the European Centre for Antimicrobial Stewardship and the Infection Society Guideline Committee for penicillin allergy delabelling, is a member of the study management committee, and is co-ordinator of UK participating sites for the International Network of Antibiotic Allergy Nations. RS is chair of the data monitoring and ethics committee for the SPACE study and is clinical director of the UK National External Quality Assessment Service for Immunology, Immunochemistry and Allergy. SS is current chair of the British Society for Immunology Clinical Immunology Professional Network and has received research funding from Kennedy Trust, Medical Research Council, EU2020 Horizon programme, Novartis, Takeda, CSL Behring, and SOBI. ST-C has received funding from the NIHR Health Protection Research Units in Healthcare Associated Infections and Antimicrobial Resistance, a partnership between the UK Health Security Agency and the University of Oxford (NIHR200915), and is a committee member of the NIHR Health and Social Care Delivery Research funding board. L-MY has received funding from the NIHR. SHP has received funding from Reckitt, Health Education England, West Yorkshire Integrated Care Board, Leeds Hospitals Charity, National Institute for Health and Care Research (NIHR), UK MS Society. SHP was a member of the Medical Research Council NIHR Efficacy and Mechanism Evaluation Board from 2012 to 2018. All other authors declare no competing interests.

**Data sharing**
The datasets generated during and analysed during this study are available upon request from the corresponding author JATS (j.sandoe@leeds.ac.uk). Codes for the analysis can be found on https://github.com/PC-CTU1/ALABAMA/tree/main.

**Acknowledgments**
The ALABAMA research team would like to thank all participants in the study and the following patient and public involvement and engagement representatives and organisations for their valuable contribution: Rosie Woollard, Amena Warner, Allergy UK, and Anaphylaxis UK. The research was supported by NIHR Local Clinical Research Networks. We acknowledge and thank the hard work and dedication of NIHR Agile Research Teams, research teams at Leeds Community Healthcare NHS Trust, Bradford District Care NHS Foundation Trust, Conexus Healthcare Wakefield, and Primary Care Sheffield, our primary care research advisor, Paul Carder, and the ALABAMA Trial Research Group, including secondary care staff at testing sites (appendix p 3) the 51 English general practice sites that participated and the ALABAMA GP Practice Advisory Group. We thank the Dental Translational and Clinical Research Unit (DenTCRU), University of Leeds team members for administrative help during trial delivery: Rory Davies, Ashna Chavda, Anna Nielsen, Gillian Dukanovic, Louise Dell'Amico, and Cheridan Morgan from the Oxford Primary Care Clinical Trials Unit, Nuffield Department of Primary Care Health Sciences, University of Oxford. We thank Bethany Shinkins for assistance with early stages of the health economics work. The research team thank the Clinical Director at The Phoenix Partnership and colleagues for their support to embed SystmOne into ALABAMA trial delivery. The authors acknowledge the contribution of the trial steering committee members and the data monitoring committee members: Michael Moore (chair of trial steering

committee), Shuayb Elkhalifa, Hazel Everitt, Beth Stuart (chair of data monitoring committee), Alice Oborne and Tony Jamieson. This work was supported by an NIHR Programme Grant for Applied Research (grant number RP-PG-1214-20007). The research is supported by the NIHR infrastructure at Leeds. JATS is supported in part by the NIHR Leeds Biomedical Research Centre (NIHR203331). The views expressed are those of the author(s) and not necessarily those of the UK National Health Service, the NIHR, or the UK Department of Health and Social Care.

**References**

1 Macy E. Penicillin and beta-lactam allergy: epidemiology and diagnosis. *Curr Allergy Asthma Rep* 2014; **14:** 476.

2 Taylor MG, Joerger T, Li Y, et al. Factors associated with penicillin allergy labels in electronic health records of children in 2 large US pediatric primary care networks. *JAMA Netw Open* 2022; **5:** e222117.

3 West RM, Smith CJ, Pavitt SH, et al. 'Warning: allergic to penicillin': association between penicillin allergy status in 2·3 million NHS general practice electronic health records, antibiotic prescribing and health outcomes. *J Antimicrob Chemother* 2019; **74:** 2075–82.

4 Solensky R, Earl HS, Gruchalla RS. Clinical approach to penicillin-allergic patients: a survey. *Ann Allergy Asthma Immunol* 2000; **84:** 329–33.

5 Blumenthal KG, Kuper K, Schulz LT, et al. Association between penicillin allergy documentation and antibiotic use. *JAMA Intern Med* 2020; **180:** 1120–22.

6 Charneski L, Deshpande G, Smith SW. Impact of an antimicrobial allergy label in the medical record on clinical outcomes in hospitalized patients. *Pharmacotherapy* 2011; **31:** 742–47.

7 Salkind AR, Cuddy PG, Foxworth JW. The rational clinical examination. Is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy. *JAMA* 2001; **285:** 2498–505.

8 McLean-Tooke A, Aldridge C, Stroud C, Spickett GP. Practical management of antibiotic allergy in adults. *J Clin Pathol* 2011; **64:** 192–99.

9 NICE. Drug allergy: diagnosis and management of drug allergy in adults, children and young people. Sept 3, 2014. https://www.nice.org.uk/guidance/cg183 (accessed Sept 10, 2014).

10 Borch JE, Andersen KE, Bindslev-Jensen C. The prevalence of suspected and challenge-verified penicillin allergy in a university hospital population. *Basic Clin Pharmacol Toxicol* 2006; **98:** 357–62.

11 Powell N, Stephens J, Kohl D, et al. The effectiveness of interventions that support penicillin allergy assessment and delabeling of adult and pediatric patients by nonallergy specialists: a systematic review and meta-analysis. *Int J Infect Dis* 2023; **129:** 152–61.

12 Armitage KF, Porter CE, Ahmed S, et al. Penicillin allergy status and its effect on antibiotic prescribing, patient outcomes and antimicrobial resistance (ALABAMA): protocol for a multicentre, parallel-arm, open-label, randomised pragmatic trial. *BMJ Open* 2023; **13:** e072253.

13 Haynes A, Brennan S, Carter S, et al. Protocol for the process evaluation of a complex intervention designed to increase the use of research in health policy and program organisations (the SPIRIT study). *Implement Sci* 2014; **9:** 113.

14 Santillo M, Roleston C, Armitage K, et al. Patients' acceptance of a penicillin allergy de-labelling programme in primary care. *BJGP Open* 2025; published online April 1. https://doi.org/10.3399/BJGPO.2024.0136.

15 Roleston C, Santillo M, Armitage KF, et al. De-labelling erroneous penicillin allergy records in general practice: healthcare professionals' experiences. *BJGP Open* 2025; published online Feb 20. https://doi.org/10.3399/BJGPO.2024.0119.

16 Armitage KF, Porter CE, Mojica-Mota R, Pavitt S, Sandoe J. ALABAMA: update to the primary outcome and cost effectiveness analysis. Dec 14, 2023. https://bmjopen.bmj.com/content/13/9/e072253.responses#alabama-update-to-the-primary-outcome-and-cost-effectiveness-analysis (accessed Dec 14, 2023).

17 Skivington K, Matthews L, Simpson SA, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. *BMJ* 2021; **374:** n2061.

18 Ahmed S, Fielding J, Porter CE, et al. Utilising primary care electronic health records to deliver the ALABAMA randomised controlled trial of penicillin allergy assessment. *Trials* 2024; **25:** 653.

19 Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and management of penicillin allergy: a review. *JAMA* 2019; **321:** 188–99.

20 Mirakian R, Leech SC, Krishna MT, et al. Management of allergy to penicillins and other beta-lactams. *Clin Exp Allergy* 2015; **45:** 300–27.

21 Santillo M, Wanat M, Davoudianfar M, et al. Developing a behavioural intervention package to identify and amend incorrect penicillin allergy records in UK general practice and subsequently change antibiotic use. *BMJ Open* 2020; **10:** e035793.

22 Little P, Stuart B, Moore M, et al. Amoxicillin for acute lower-respiratory-tract infection in primary care when pneumonia is not suspected: a 12-country, randomised, placebo-controlled trial. *Lancet Infect Dis* 2013; **13:** 123–29.

23 Savic L, Gurr L, Kaura V, et al. Penicillin allergy de-labelling ahead of elective surgery: feasibility and barriers. *Br J Anaesth* 2019; **123:** e110–16.

24 Harper HM, Sanchez M. Review of pharmacist driven penicillin allergy assessments and skin testing: a multi-center case-series. *Hosp Pharm* 2022; **57:** 469–73.

25 Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis* 2016; **62:** e51–77.

26 WHO. Antimicrobial stewardship interventions: a practical guide. Copenhagen: WHO Regional Office for Europe, 2021.

27 Chua KYL, Vogrin S, Bury S, et al. The penicillin allergy delabeling program: a multicenter whole-of-hospital health services intervention and comparative effectiveness study. *Clin Infect Dis* 2021; **73:** 487–96.

28 Macy E, Shu YH. The effect of penicillin allergy testing on future health care utilization: a matched cohort study. *J Allergy Clin Immunol Pract* 2017; **5:** 705–10.

29 Rose MT, Holmes NE, Eastwood GM, et al. Oral challenge vs routine care to assess low-risk penicillin allergy in critically ill hospital patients (ORACLE): a pilot safety and feasibility randomised controlled trial. *Intensive Care Med* 2024; **50:** 913–21.

30 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.

31 Andrews A, Budd EL, Hendrick A, et al. Surveillance of antibacterial usage during the COVID-19 pandemic in England, 2020. *Antibiotics (Basel)* 2021; **10:** 841.

32 NICE. Pneumonia (community-acquired): antimicrobial prescribing. NICE guideline NG138. Sept 16, 2019. https://www.nice.org.uk/guidance/ng138 (accessed Sept 20, 2019).

33 NICE. COVID-19 rapid guideline: managing suspected or confirmed pneumonia in adults in the community. NICE guideline NG165. April 3, 2020. https://www.nice.org.uk/guidance/ng165 (accessed April 23, 2020).

34 Kulalert P, Phinyo P, Chiriac AM, et al. Is a prolonged drug provocation test better than a single-day drug provocation test? A systematic review and meta-analysis. *J Allergy Clin Immunol Pract* 2024; **12:** 431–48.