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Allergy, antibiotics and microbial resistance

Submission date
28/01/2019

Recruitment status
No longer recruiting

Registration date
14/02/2019

Overall study status
Completed

Last Edited
04/10/2024

Condition category
Injury, Occupational Diseases, Poisoning

[X] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Antibiotics are important medicines for fighting infections caused by bacteria. Their widespread use has caused a worrying rise in antibiotic resistant bacteria, which are bacteria that are harder to control or kill with antibiotics. Patients with infections caused by antibiotic resistant bacteria are often ill for longer and have an increased risk of serious harm, including death. We can slow the spread of resistant bacteria by using antibiotics more carefully. Penicillins are an important group of antibiotics that are recommended and the best treatment for many infections. Doctors will avoid prescribing penicillin for their patients who have a “penicillin allergy label” in their health records. These patients are usually prescribed different types of antibiotics for their infections. There is concern that these non-penicillin antibiotics may not work as well as penicillins, may cause more side effects more often (including killing more of the body’s “helpful” bacteria), and may be more expensive. About 9 out of 10 people who have a record of penicillin-allergy are found to be not truly allergic to penicillin when thoroughly tested. This means they could safely take penicillins. The aim of this study is to find out whether people with a penicillin-allergy record in their GP health records really do have an allergy by carrying out specialist testing, and to see if this reduces the number of patients wrongly labelled as penicillin allergic. The researchers will find out if this results in better use of antibiotics and fewer days of symptoms when patients are prescribed antibiotics for infection.

Who can participate?
Patients aged over 18 who have taken an antibiotic in the previous 12 months and whose medical records state that they are allergic to penicillin antibiotics

What does the study involve?
Participants are randomly allocated to either usual care (with monitoring of any symptoms following an antibiotic prescription) or penicillin allergy testing. Participants allocated to the PAAP allergy testing are required to attend a hospital clinic for skin testing and/or oral challenge. 4 – 6 and 28 – 30 days after completing the testing participants answer short phone calls from the research team to check for any delayed reactions and complete a short questionnaire. The first 96 study participants receive four short phone calls from the research team, monthly, during the first four months of their participation, to check for again for any possible delayed reaction to the test. For the following 12 months each time participants attend their GP surgery with an infection that requires antibiotics they complete a diary about their symptoms for 28 days or until they feel better. Participants are also required to answer two

phone calls by the research team, 2-4 and 28-30 days after visiting their GP with an infection requiring antibiotic treatment, and one phone call after 12 months, each phone call requires them to answer a short questionnaire.

What are the possible benefits and risks of participating?
There may not be any direct benefit to participants, but if their penicillin allergy status is changed, first-line penicillin treatment for many infections can resume. It is also hoped the outcomes of this study will improve access to penicillin allergy testing; improve patient outcomes related to infection e.g. fewer days of symptoms; reduce antibiotic prescriptions and reduce resistant bacteria; and benefit the NHS by saving GP time and improving value for money. There is a small risk from skin testing and oral challenge testing and a risk from any antibiotics that are prescribed as part of usual clinical care during the time of the study. Skin testing is generally safe and severe reactions following testing are rare. For example, five patients (0.5%) had severe reactions in one eight-year study including 998 skin tests. Severe reactions to an oral challenge test in patients with negative skin-tests are uncommon but do occur. Among 580 orally challenged patients with a history of non-serious skin reactions to penicillin, 14 had reactions, 11 of which were early and 3 delayed. A reaction was more likely if the allergy report was within 15 years. A series of increasing drug doses is used during the oral challenge, and it will take place in a specialist unit with facilities to deal with any potential severe allergic reactions. Participants will be called 4– 6 days after the appointment by a study research nurse to check how they are feeling and if they have had any delayed side effects. Penicillin allergy testing is routinely carried out in the NHS, but it carries a very small risk of anaphylaxis and death. This risk will be minimised by excluding any patient with a prior history suggestive of anaphylaxis or a previous serious reaction.

Where is the study run from?
University of Leeds and the University of Oxford (UK)

When is the study starting and how long is it expected to run for?
Recruitment for the pilot study is starting in April 2019 and participants will be followed up for a minimum of 3 months. If the study continues to the main trial, recruitment will start in February 2020 and participants will be followed up until February 2024. The overall trial end date is 29th February 2024.

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
1. Catherine Porter
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2. Kelsey Armitage
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Study website
https://www.phc.ox.ac.uk/research/institutes-units/phctrials/trial-portfolio/alabama-allergy-antibiotics-and-microbial-resistance

Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
NCT04108637

Secondary identifying numbers
40811

Study information

Scientific Title
Penicillin allergy status and its effect on antimicrobial prescribing, patient outcomes, and antimicrobial resistance

Acronym
ALABAMA

Study objectives
Penicillins are recommended first line treatment for many infections; they are safe, effective, narrow spectrum and inexpensive. Approximately 10% of the population are pen-allergic according to their medical records, but <10% of these are likely to be truly allergic. Pen-allergy records drive prescribing towards alternative broad spectrum antimicrobials that contribute to increased antimicrobial resistance (AMR) and poorer patient outcomes.

The aim of ALABAMA is to determine whether a complex intervention for verifying pen-allergy labels in primary care health records (eHR) can safely reduce the proportion of patients labelled as pen-allergic and lead to improved (safe/appropriate) prescribing of recommended first line antimicrobials, thereby improving patient health outcomes.

Ethics approval required

Ethics approval required

Ethics approval(s)
Approved 29/01/2019, London Bridge REC (Skipton House, 80 London Road, London, SE1 6LH, United Kingdom; +44 (0)20 7104 8222; nrescommittee.london-londonbridge@nhs.net), ref: 19/LO/0176

Study design
Randomized; Both; Design type: Process of Care, Psychological & Behavioural, Complex Intervention, Management of Care, Cross-sectional

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
GP practice

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Penicillin allergy

Interventions
During their call with the research team, participants will be asked if they have taken any antibiotics in the previous two weeks, if they have, the randomisation/baseline call will be postponed until the participant has been free of antibiotic use for two weeks. The research team will arrange another call for when the participant is free of antibiotics use for two weeks. During the call, the participants will be asked to complete the baseline assessment and the member of the research team will perform randomisation. Randomisation will be performed using Sortition (PC-CTU's in-house online randomisation system) according to the current version of the SOP PC-CTU_SOP_IT104. Allocation will be minimised by general practice, age, number of antibiotic prescriptions/year, and number of QOF registered diseases, to ensure balance of allocation of these baseline covariates. Patients will be randomised to either usual care (with monitoring of any symptoms following an antibiotic prescription) or the PAAP intervention arm using an allocation ratio of 1:1. Both the participants and the recruiter will know which arm they have been randomised into. The trial statistician will remain blinded to treatment allocation when performing the final analysis. Unblinding of the allocation will take place in accordance of the SOP PC-CTU_SOP_ST106.

Patients who are randomised to the PAAP arm will be asked to undergo penicillin allergy testing, involving: penicillin allergy history; skin testing and/or oral challenge test. Patients will receive

their allergy test result by a letter and/or email. Practices will be informed of the results and will be asked to ensure that the patient's electronic health records are updated. Antibiotic prescriptions will be monitored as well as other health outcomes.

Patients will be followed up for 4 months for the feasibility study and, following a stop go, 12 months in the main trial. When patients are prescribed an antibiotic, an alert will be sent to the trial team who will follow up the participant for 28 days after each event. At the end of the follow up period their health records in primary and secondary care will be reviewed to ensure all antibiotic events and outcomes are captured.

GPs will be participants within the process evaluation of ALABAMA. GPs will be invited to complete questionnaires to understand their knowledge and beliefs about penicillin allergy testing and referring patients for testing. A subset of GPs will be invited to take part in an interview at the end of the trial to discuss their experiences.

Intervention Type
Other

Primary outcome measure
Current primary outcome measure as of 22/03/2024:

The proportion of participants who receive prescriptions for a penicillin when attending for predefined conditions where a penicillin is the first-line recommended antibiotic (APPENDIX G) up to 12 months post randomisation (SystmOne report/primary care notes review/secondary care notes review/report, patient follow-up calls).

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Previous primary outcome measure:

Treatment “response failure” defined as: re-presentation with worsening or non-resolving symptoms following treatment with an antibiotic up to 28 days after initial antibiotic prescription (including re-prescription of antibiotic within 28 days of an index prescription) for predefined conditions (TPP/notes review), over the year subsequent to randomisation

Secondary outcome measures
Current secondary outcome measures as of 22/03/2024:

1. Treatment “response failure” defined as:
Re-presentation with worsening or non-resolving or new symptoms following treatment with an antibiotic up to 28 days after initial antibiotic prescription (including re-prescription of antibiotic within 28 days of an index prescription) for predefined infections (SystmOne report, diary), up to 12 months post randomisation.
2. Duration of symptoms rated ‘moderately bad’ or worse by patients after antibiotic treatment (diary/research nurse phone calls)
3. Total antibiotic use (measured by number of days treatment, number of prescriptions and Defined Daily Dose (DDD).), and analysed by penicillin/non-penicillin and antibiotic class (SystmOne report/primary care notes review/secondary care notes review).
4. Number of hospital admissions and length of hospital stays (Hospital Episode Statistic (HES) /secondary care notes review)
5. Mortality rates between intervention arms (primary care notes review/secondary care notes HES-ONS/SystmOne Report)

6. Number of patients with MRSA infection/new colonisation (primary care notes review /secondary care notes review/SystmOne report)
7. Number of patients with Clostridioides difficile infection (SystmOne report/primary care notes review/secondary care notes review)
8. Healthcare professional and patient interviews to explore patient and clinician views and experiences of penicillin allergy testing, test results and future antibiotic use.
9. Healthcare professional and patient interviews to explore patient and clinician experiences of trial procedures.
10. Change in self-reported behaviour and influences on behaviour by patients.
11. Self-reported health/QoL outcome: EQ-5D-5L™ will be used as a standardised instrument for measuring health outcome at baseline and 1 year. For those that receive antibiotics for pre-defined infections, EQ5D-5L will be collected on day 2-4 and day 28-30 after antibiotic treatment. NHS health resource use will be measured through primary and secondary care notes review, and through linked HES data.
12.1. The proportion of ALABAMA participants whose labels are removed from the primary care medical eHR record allergy section at 3 months post randomisation.
12.1. The proportion of ALABAMA participants whose labels were removed at 3 months and remain removed from the primary care medical eHR record allergy section up to 12 months post-randomisation.

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Previous secondary outcome measures as of 31/05/2023:

1. Effects of PAAP on symptom duration measured using duration of symptoms rated 'moderately bad' or worse by patients after antibiotic treatment (diary/research nurse telephone calls at Day 1 – 28 day symptom diary after the first antibiotic prescription identified as a primary event. This will also be collected on days 28-30 by phone call for every antibiotic prescription identified as a primary event
2. Effects of PAAP on total antibiotic prescribing measured using total antibiotic use (number of days of treatment, Defined Daily Dose (DDD)). Total number of penicillin and non-penicillin antibiotic prescriptions (number of days of treatment, DDD, and analysed by antibiotic class) (SystmOne report/notes review/secondary care notes review). Total antibiotic use for pre-defined infections (number of days treatment, DDD –defined daily dose) at 12-month post-randomisation notes review (continues annually until the end of the trial)/Secondary care notes review
3. Effects of PAAP on hospital admissions and length of hospital stays measured using the number of hospital admissions and length of hospital stays (Hospital Episode Statistic (HES) /secondary care notes review) at 12-month post-randomisation (continues annually until the end of the trial)
4. Effects of PAAP on mortality rates measured using mortality rates between intervention arms at 12 monthly notes review post-randomisation (continues annually until the end of the trial)
5. Effects of PAAP on Meticillin-resistant Staphylococcus aureus (MRSA) infection/colonisation measured using the number of patients with MRSA infection/colonisation at 12 months post-randomisation notes review (continues annually until the end of the trial)
6. Effects of PAAP on Clostridioides difficile infection measured using the number of patients with Clostridioides difficile infection at 12-month post-randomisation notes review (continues annually until the end of the trial).
7. To explore patient and clinician views and experiences of penicillin allergy testing, test results and future antibiotic use measured using GP and patient interviews. Qualitative Interviews for GPs once their practice has recruited a proportion of patients to the trial and participants once they have received their PAAP result

8. (Process evaluation) To explore patient and clinician experiences of trial procedures measured using GP and patient interviews. Qualitative interviews for GPs once their practice has recruited a proportion of patients to the trial and participants once they have received their PAAP result
9. To measure the influences on patient behaviour change regarding consuming penicillin following a negative test result measured using change in self-reported behaviour and influences on behaviour by patients at Baseline, D28 – 30 post-PAAP, D2 - 4 post-antibiotic episode
10. Cost-effectiveness for the PAAP intervention compared to usual care measured using Self-reported health/QoL outcome: EQ-5D-5L™ will be used as a standardised instrument for measuring health outcome at baseline and 1 year. For those that receive antibiotics, EQ5D-5L will be collected on days 2-4 and days 28-30 after antibiotic treatment. NHS health resource use will be measured through primary and secondary care notes review.

Previous secondary outcome measures:

1. Duration of symptoms rated 'moderately bad' or worse by patients after antibiotic treatment, measured on Day 1 – 28 diary after each antibiotic prescription and at day 28-30 by phone call
2. Total antibiotic use (number and ADQ – average daily quantity) and total number of penicillin and non-penicillin antibiotic prescriptions (number and ADQ) measured at 12 month post-randomisation notes review (continues annually until end of study)/secondary care notes review
3. Number of hospital admissions and length of hospital stays, measured using Hospital Episode Statistics (HES)/secondary care notes review 12 month post-randomisation (continues annually until end of study)
4. Mortality rates measured using ONS/12 monthly notes review post-randomisation (continues annually until end of study)
5. Number of patients with MRSA infection/colonisation, measured at 12 month post-randomisation notes review (continues annually until end of study)
6. Number of patients with Clostridium difficile infection, measured at 12 month post-randomisation notes review (continues annually until end of study)
7. Patient and clinician views and experiences of penicillin allergy testing, test results and future antibiotic use, assessed using qualitative interviews with GPs once their practice has recruited a proportion of patients to the trial and participants once they have received their PAAP result
8. Patient and clinician experiences of trial procedures, assessed using qualitative interviews with GPs once their practice has recruited a proportion of patients to the trial and participants once they have received their PAAP result
9. Change in self-reported behaviour and influences on behaviour by clinicians and patients, measured using GP questionnaire (throughout trial) and participant allergy belief questionnaires (baseline, days 28 – 30 post-PAAP, days 2 -4 post-antibiotic episode)
10. Cost effectiveness for the PAAP intervention compared to usual care, measured using self-reported health/QoL outcome and NHS health resource use. EQ-5D-5L™ will be used as a standardised instrument for measuring health outcome at baseline and 12 months post randomisation and on day 2 – 4 post antibiotic episode (endpoint is 12 months post randomisation)

Overall study start date
01/09/2017

Completion date
29/02/2024

Eligibility

Key inclusion criteria
Current inclusion criteria as of 22/03/2024:

1. Participant is willing and able to give informed consent for participation in the study
2. Male or female, aged 18 years or above
3. Penicillin allergy (or sensitivity) record of any kind in their electronic health record
4. Prescribed systemic antibiotics, either: penicillin, cephalosporin, tetracycline, quinolone, macrolide, glycopeptide, aminoglycoside, oxazolidinone, monobactam or carbapenem class antibiotic or fosfomycin, nitrofurantoin, trimethoprim, clindamycin, rifampicin, colistin, metronidazole in the previous 24 months

NB Patients with a penicillin allergy record and a recent penicillin prescription would still be eligible because their allergy status will need assessment and records correcting if necessary.

Previous inclusion criteria:

1. Participant is willing and able to give informed consent for participation in the study
2. Male or female, aged 18 years or above
3. Penicillin allergy (or sensitivity) record of any kind in their electronic health record
4. Receipt of either: penicillin, cephalosporin, tetracycline, quinolone or macrolide class antimicrobial or fosfomycin, nitrofurantoin, trimethoprim, clindamycin in the previous 12 months

NB Patients with a penicillin allergy record and a recent penicillin prescription would still be eligible because their allergy status will need assessment and records correcting if necessary.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 2090; UK Sample Size: 2090

Total final enrolment
823

Key exclusion criteria
Current exclusion criteria as of 22/03/2024:

1. Life expectancy estimated < 1 year by GP
2. Unable to attend hospital clinic where allergy testing takes place
3. Unsuitable for entry into testing pathway because:
3.1. Allergy history consistent with anaphylaxis to penicillin
3.2. History of toxic epidermal necrolysis, Stevens-Johnson syndrome, Drug reaction with eosinophilia and systemic symptoms (DRESS) or any severe rash which blistered or needed hospital treatment, and acute generalised exanthematous pustulosis precipitated by a penicillin
3.3. Has been formally tested for penicillin allergy in the past and been found to be penicillin allergic
3.4. History of brittle asthma (had a course of steroids in the past 3 months) or unstable coronary artery disease, or dermographism or other severe/poorly controlled skin conditions
3.5. Considered unsuitable for trial participation by the GP e.g. because of chaotic lifestyle
4. Pregnant
5. Breastfeeding mothers
6, Currently taking beta blocker medication and unable to temporarily withhold these on the day of penicillin allergy testing
7. Currently taking (or recently taken) systemic steroids and unable to top these for 10 days pre-testing
8. Currently taking antihistamines and unable to temporarily withhold these for 72 hours pre-testing

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Previous exclusion criteria:

1. Life expectancy estimated < 1 year by GP
2. Unable to attend immunology clinic
3. Unsuitable for entry into testing pathway because:
3.1. Allergy history consistent with anaphylaxis to penicillin
3.2. History of toxic epidermal necrolysis, Stevens-Johnson syndrome, Drug reaction with eosinophilia and systemic symptoms (DRESS) or any severe rash which blistered or needed hospital treatment, and acute generalised exanthematous pustulosis precipitated by a penicillin
3.3. Previous specialist investigation for penicillin allergy
3.4. History of brittle asthma (had a course of steroids in the past 3 months) or unstable coronary artery disease, or dermographism or other severe/poorly controlled skin conditions
3.5. Considered unsuitable for trial participation by the GP e.g. because of chaotic lifestyle
4. Pregnant/planning to become pregnant during the course of the study
5. Breastfeeding mothers
6. Currently receiving or due to start immunosuppressive medication
7. Currently taking (or recently taken, within 10 days) steroids
8. Currently taking antihistamines and unable to stop these for 4 days pre-testing

Date of first enrolment
17/09/2019

Date of final enrolment
31/07/2023

Locations

Countries of recruitment

United Kingdom

Study participating centre
Not confirmed yet
United Kingdom
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Sponsor information

Organisation
University of Leeds

Sponsor details
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Sponsor type
University/education

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Government

Funder Name
NIHR Central Commissioning Facility (CCF); Grant Codes: RP-PG-1214-20007

Results and Publications

Publication and dissemination plan

The protocol is not published yet. The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the NIHR. Authorship will be determined by the CI in accordance with the ALABAMA Publication Policy developed with the Trial Management Group in accordance with the ICMJE guidelines and other contributors will be acknowledged. Planned publication in a high-impact peer reviewed journal around 1 year after the overall trial end date.

Intention to publish date
01/11/2024

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Dr Jonathan Sandoe, j.sandoe@leeds.ac.uk.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Other publications	results of mixed-methods process evaluation embedded within the ALABAMA trial	03/06/2022	25/01/2023	Yes	No
HRA research summary			26/07/2023	No	No
Protocol article		04/09/2023	05/09/2023	Yes	No
Statistical Analysis Plan	version 1.0	09/04/2024	18/04/2024	No	No
Other files	version 1.15	17/06/2024	22/07/2024	No	No
Protocol file	version 14.0	16/11/2023	23/07/2024	No	No
Other publications	Utilising primary care electronic health records to deliver the ALABAMA randomised controlled trial of penicillin allergy assessment	03/10/2024	04/10/2024	Yes	No