Exploring factors associated with antimicrobial prescribing in adults with Acute Respiratory Infection (ARI) amongst UK secondary care prescribers and the potential utility of host response testing to improve use: a questionnaire-based survey.

Chief & Principal Investigator:

Professor Tristan Clark

Co-investigators:

Dr Alex R Tanner

Dr Rebecca Wong

Professor Ingrid Muller

1. Protocol overview

1.1 Research reference numbers

Sponsor's reference number: RHM MED 2107

IRAS number: 359861
REC Reference: 25/HRA/2717
ERGO ID: 106697

1.2 Protocol version number and date

1.0 17th June 2025

1.3 Sponsor

University Hospital Southampton NHS Foundation Trust

1.4 Title of the study:

Exploring factors associated with antimicrobial prescribing in adults with Acute Respiratory Infection (ARI) amongst UK secondary care prescribers and the potential utility of host response testing to improve use: a questionnaire-based survey.

2.0 SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:

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Name (please print):

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Position:

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Chief Investigator:

Signature: Date:

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Name: (please print):

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3.0 Key Trial contacts

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Joint-sponsor(s)/co-sponsor(s)	N/A

4.0 Trial Summary

Study Title	Exploring factors associated with antimicrobial prescribing in adults with Acute Respiratory Infection (ARI) amongst UK secondary care prescribers and the potential utility of host response testing to improve use: a questionnaire-based survey.
Short title	Exploring antibiotic prescribing in ARI
Study Design	Mixed methods (Quantitative and Qualitative), cross-sectional, questionnaire-based survey
Study Participants	Adults > 18 years old, medical physicians, prescribing Advanced Care Practitioners and Nurse Practitioners working in (Infectious Diseases; Respiratory Medicine; Acute Medicine; Geriatric Medicine; General Medicine) and Emergency Department physicians working in the National Health Service caring for adult (>18 years old)

	patients presenting to hospital with acute respiratory illness.
Planned Size of Sample (if applicable)	Focus Group: 4-12 Questionnaire arm: 100-200
Follow up duration (if applicable)	N/A
Planned Study Period	Focus Groups: July 2025 – September 2025 Questionnaire data collection: September 2025 - November 2025 Data Analysis: November 2025 – December 2025 Write up: December 2025 – February 2026
Research Question/Aim(s)	1.To explore key factors influencing antibiotic prescribing decisions by secondary care prescribers in adult patients presenting to ED with acute respiratory illness. 2. To explore which characteristics of a theoretical host response diagnostic test, secondary care prescribers would most value most. 3. To explore, through case vignettes, whether the results of host response-based diagnostic tests might alter prescribing decisions in adults with ARI.

5.0 Funding and resources

FUNDER(S)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
Tristan Clark UHS PI Fund	Cost for using SurveyMonkey™ and to distribute the questionnaire.

6.0 Role of Trial Sponsor

The Sponsor is University Hospital Southampton NHS Foundation Trust (UHS), which is the organisation that is taking legal responsibility for the trial.

6.1 Protocol Contributors

UHS as the primary sponsor have no role, responsibility or control in study design, conduct, data analysis and interpretation or writing or dissemination of results.

7.0 Background

Patients presenting to emergency departments are frequently given antibiotics that they do not need as a lot of ARI is caused by viruses.

Previous studies show that the vast majority of adult patients presenting to hospital with acute respiratory illness (ARI) receive antibiotics.[1,2] However, much of this is unnecessary, as around half of episodes of ARI are caused by viruses.[2] This unnecessary antibiotic use is directly harmful to patients as it is associated with adverse events including C.difficile infections[3] and also promotes the development of antimicrobial resistance (AMR). AMR is one of the most serious threats to human health and measures to combat it are a global priority.[4]

Testing for the presence of viruses themselves in ARI does not reduce antibiotic use

Meta-analyses of trials evaluating the impact of rapid molecular testing for respiratory viruses in hospital inpatients and EDs have demonstrated improvements in patient care across a range of outcomes, including antiviral use and infection control practices.[5–7] However, the impact on unnecessary antibiotic use has been minimal.[5,8]

Understanding the factors that influence physician antibiotic prescribing decisions in patients with viral ARI are imperative to formulate effective strategies to reduce unnecessary antibiotic use and combat AMR

A large multi-centre prospective cohort study performed during the SARS-CoV-2 pandemic revealed that bacterial co-infection in patient's admitted to hospital with Covid-19 was rare. Despite this, there were high rates of use of broad spectrum antibiotics.[9] There is growing evidence that, in patients hospitalised with SARS-CoV-2 and other respiratory viral infections, there is no survival benefit from use of antibiotics.[10–13]

Previous human factors research suggests that concern over possible bacterial co-infection is a key driver of antibiotic use in viral ARI. Prescribing decision are also influenced by multiple inter-related factors including; an individual's clinical experience, the perceived risk of missing a bacterial infection in an individual patient, departmental culture and perceived patient expectations.[14]

Therefore, to begin to effectively address antibiotic overuse in viral ARI and combat AMR, a more detailed understanding of how human factors interplay with patient symptoms, signs and biochemical and radiological test results is urgently needed.

Novel Combination host response biomarker tests may be able to distinguish bacterial and viral ARI more accurately

Combined host response testing distinguishing between viral and bacterial infection using separate host immune response biomarkers (either via detecting proteins or host gene expression using mRNA is emerging as a potential diagnostic approach to direct

and reduce unnecessary antibiotic use.[19] One such test is the TriVerity Acute Infection and Sepsis Test (Inflammatix, Sunnyvale, CA, USA), which uses an isothermal reverse-transcribed loop-mediated amplification (qRT-LAMP) assay to measure levels of 29 host mRNAs in blood and incorporates machine learning to calculate 3 separate scores predicting the likelihood of bacterial infection, viral infection and illness severity.[19] TriVerity has been granted Food and Drug Administration (FDA) approval and likely will have CE (IVDR) marking in 2025 and has a turnaround time of 30 minutes on the MyRNA point-of-care testing platform.

Data from multiple studies suggest that is accurate in differentiating viral and bacterial infection including ARI, in multiple settings including ED.[19,20] However, there have been no studies evaluating impact on antibiotic use. In order to design these trials, a deeper understanding of factors underlying antibiotic use and of how the results from these tests might influence prescribing decision are therefore urgently needed.

Why this research is important?

ARI is the commonest reason for antibiotic use in ED and around half of this is unnecessary

Antibiotics are very frequently prescribed to patients presenting to the ED with ARI but around half of these prescriptions are thought to be inappropriate with adults more likely to be prescribed inappropriate antibiotics than children.[21] Recent UK trial data suggests that around 80-90% of adult patients presenting with unselected ARI receive antibiotics in ED.[2,7]

AMR is driven by unnecessary antibiotic use and is a global threat

Bacterial resistance develops in response to selective pressure associated with all antibiotic prescribing but is accelerated by inappropriate use.[22] A substantial increase in global rates of infections caused by resistant pathogens, in combination with limited new antimicrobial agents in development, has raised concerns of an impending 'post-antibiotic era' with catastrophic consequences for human health.[4] AMR is now recognised as one of the biggest threats to global health and efforts to preserve the effectiveness of antibiotics through antibiotic stewardship are a priority.

ED and AMU are a priority area for antibiotic stewardship

As the interface between the community ED and AMU are priority areas for antimicrobial stewardship[1,23] as antibiotics started in these departments are usually continued in other departments when hospitals are moved within the hospital or when discharged home.[1] Therefore, understanding factors which influence doctors and other secondary care prescribers decisions to prescribe antibiotics who work in ED and AMU in ARI is critical to help design future strategies to reduce AMR.

Review of existing evidence

A systematic literature review of published research was undertaken using terms related to qualitative studies which explored factors influencing antibiotic prescribing. A recent meta-synthesis study using theoretical domains demonstrated a number of human factors influencing antibiotic prescribing habits including; clinical uncertainty regarding the underlying diagnosis, fear of adverse outcomes if antibiotics were withheld,

prioritising perceived patient safety and influences of work hierarchies and concern about being criticised.[18] In another study evaluating the association between presence of specific signs and symptoms in patient with ARI and antibiotic prescribing, fever, purulent sputum and clinical signs on respiratory examination, were all factors associated with antibiotic use.[16–18]

Within primary care, previous studies have identified that clinician time pressure, C-reactive protein levels, patient expectations, and clinical examination findings are major factors in antibiotic use.[16] A Danish study of General Practitioners' found C-reactive protein, and the patient's general condition to be the two factors which most influenced prescribing practices.[15]

The current literature therefore provides a strong rationale for urgent studies to explore through both qualitative and quantitative methods the factors associated with antibiotic prescribing in ED to inform the design of antibiotic stewardship studies including those using novel host response tests to guide antibiotic use.

8.0 Aims, objectives and outcome measures

8.1 Aims and objectives

To explore factors associated with antibiotic prescribing by secondary care prescribers in adult patients with acute respiratory illness, where viruses are detected. Also, to investigate the potential of novel host response test results to influence prescribing.

Objectives

1. Explore factors associated with prescribing antibiotics in adult patients presenting to ED with ARI where viruses are detected

2. Explore the opinions of secondary care prescribers on the importance of different characteristics of a theoretical host response in-vitro diagnostic test

3. Explore the potential utility of host response testing to influence antibiotic prescribing decisions in adults presenting to ED with ARI where viruses are detected

Outcome measures (exploratory)

1. Using focus groups and questionnaires, describe and rank factors associated with antibiotic use in adults presenting to ED with ARI where viruses are detected. Also, explore through thematic analysis the detailed reasons underpinning these factors.

2. Using focus groups and questionaries, describe and rank a list of desirable characteristics of a new theoretical host response diagnostic test. Additionally, explore evaluate through thematic analysis the detailed reasons underpinning these factors.

3. In adults presenting to hospitals with ARI, who have tested positive for viral respiratory pathogens, describe the impact on antibiotic use of a theoretical host response test. This will be done using a questionnaire containing case vignettes covering a range of clinical

scenarios. Thematic analysis will be used to identify the detailed reasons underpinning any change in prescribing behaviours following host-response testing being available.

8.2 Study design and methods:

8.2.1 Focus groups:

To help inform the design of the cross-sectional questionnaire, we will conduct focus group interviews with key stake holder groups (Medical Consultants, Registrars, Resident Doctors and prescribing Nurse Practitioners and Advanced Care Practitioners) at UHS who work in Acute medicine, Emergency medicine, Infectious diseases, Elderly care, General medicine and Respiratory medicine, to understand what factors they consider important when making antibiotics prescribing decisions in a patient with ARI who have a viral pathogen detected. We will also determine which characteristics of new host response tests they would consider most important in assisting with these decisions.

The focus groups, of maximum size of four, will be led by one of the study team and participants will be invited through a group email sent through the trusts HR department. Purposive sampling will be performed by screening basic demographic data (seniority, ethnicity and speciality) of those who express interest. The focus group will be performed, and audio recorded virtually on MS Teams. Within the transcript, participants identities will be kept confidential, but their seniority, ethnicity and medical speciality will be noted.

The recording of the focus groups will be transcribed using MS Teams. Analysis will take place using reflective thematic analysis, and will include; reading and familiarisation of the transcripts, noting and recording initial themes and then conducting systematic and detailed open coding using ethnographic research software. The coding of the first set of transcripts will generate an initial coding framework, which will be discussed with members of the research team. This will be further developed and refined as analysis proceeds. The research team will also critically review and refine the categories and themes emerging from the data, to ensure trustworthiness and increase rigour, before defining and naming them. Focus group data collection will stop once information power has been reached. The audio recordings will be stored on UHS Servers through the interviews being performed via UHS MS Teams application and transcript data will be stored on UHS Servers, which will only be accessible to the research team.

8.2.2 Questionnaire design and dissemination

After thematic analysis from the focus groups, a detailed literature search will inform the options participants can select when answering the questionnaire on factors which influence antibiotic prescribing habits in ARI and desirable characteristics of host response tests. The questionnaire will be designed on an easy to use and accessible online platform called SurveyMonkey™. The questionnaire will be piloted at UHS after development to ensure useability and validity and may be potentially modified depending on feedback. The method for piloting will include sending out 5-20 questionnaires locally at UHS to the relevant departments of interest, with the answers

being reviewed to ensure usability and participants will be invited to email their feedback on the survey to the study team. Once it has been finalised after piloting, it will then be emailed to Doctors and prescribing Nurse Practitioners and Advanced Care Practitioners working in the Emergency department, Acute medicine, Respiratory medicine, Infectious diseases, Geriatric medicine, General medicine through HR departments of trusts locally (UHS, Hampshire Hospital NHS Foundation Trust, Queen Alexander Hospital). An email inviting participants to take part in these trusts with a link to the questionnaire will be sent monthly for 3 months in total to ensure maximal engagement.

8.3 Participant eligibility criteria for inclusion into the focus groups

Inclusion criteria

- Qualified prescribing Medical Doctor, Nurse practitioner or Advanced Care Practitioner, working within secondary care in the NHS whose primary patients are ≥18 years of age
- Participants must regularly assess patients presenting to hospital with ARI
- Participants must work in the following specialities: Emergency medicine, Acute medicine, Respiratory medicine, Geriatric medicine, Infectious diseases, General medicine

Exclusion criteria for involvement in the focus groups

Not fulfilling the above criteria

8.4 Sample and Recruitment for focus groups arm

Participants for the focus group will be emailed via trust wide HR email to the 'medicine division' to ensure only relevant medical specialities are approached. Review of the seniority of the Doctors, Nurse Practitioners and Advanced Care Practitioners applying to participate in the focus groups will be undertaken to ensure a balanced mix of participants. UHS will be chosen as the site for the focus groups and development of the questionnaire, for convenience. Focus group recruitment will stop once thematic data saturation point has been reached.

8.5 Participant eligibility criteria for inclusion into the questionnaire survey arm

- Qualified prescribing Medical Doctor or Nurse Practitioner or Advanced Care Practitioner working within secondary care in the NHS whose primary patients are ≥18 years of age at UHS, QAH, HHFT
- Participants must regularly assess adult presenting to hospital with ARI
- Participants must work in the following specialities: Emergency medicine, Acute medicine, Respiratory medicine, Geriatric medicine, Infectious diseases, General medicine

Exclusion criteria for involvement in the focus groups

- Not fulfilling the above criteria

8.6 Consent for focus group interviews

Those who kindly agree to attend the focus groups will have time to read the PIS and then will provide written consent via an electronic consent form to take part within the focus groups. Additionally, within the email advertising the study, the PIS will be attached to allow individuals time to consider the information.

8.7 Consent for questionnaire survey

A poster inviting participants to take part in the questionnaire will be included in the email to participants invited to take part, as well as the email addresses for the study team to allow participants to ask questions.

The inclusion and exclusion criteria to undertake the questionnaire study is explained in the opening question of the questionnaire and consent to take part will be confirmed before completing the questionnaire.

8.8 Withdrawal criteria

The participant must remain free to withdraw at any time from the trial without giving reasons and must be provided with a contact point where he/she may obtain further information about the trial. Subject withdrawal of consent from the trial must be explicitly documented in the source documents.

The CI/PI may withdraw a participant from the study for the integrity of the research study, or on the advice of the Sponsor's representative (Research & Development (R&D) department). Any participant who is withdrawn from the study has the options of withdrawing and having any data collected so far retained or withdrawing and having their data destroyed. A note to file would normally be sufficient to record any withdrawal.

9.0 Statistics and data analysis

9.1 Sample size and analysis plan for the focus group arm

Analysis will take place using reflexive thematic analysis, and will include reading and familiarisation of the transcripts, noting and recording initial themes and then conducting systematic and detailed open coding. The coding of the first set of transcripts will generate an initial coding framework, which will be discussed with members of the research team. This will be further developed and refined as analysis proceeds. The research team will also critically review and refine the categories and themes emerging from the data, to ensure trustworthiness and increase rigour before defining and naming them. Focus group data collection will stop once information power has been reached.

9.2 Sample size and statistical analysis plan for the questionnaire arm

The SurveyMonkey™ questionnaire will be emailed monthly to the respective Trusts for three months to ensure maximal engagement. Sample size was calculated to be 100 completed responses to achieve an adequate range of views. A confidence interval approach was used to determine a target sample size for the survey. The most conservative sample size is given by assuming that 50% of participants would choose each response. Based on a 95% confidence interval +/- 10%, a minimum of 97 participants would be needed. Therefore, the lower target for the survey was 100 participants and upper target of 200.

The structure and design of the questionnaire will be reviewed by a qualitative statistician to ensure robust and rigorous design. Descriptive demographic data (District General Hospital vs Tertiary referral hospital, years of practice, grade, speciality) will be collected and summarised using descriptive statistics. Friedman's Test will be performed to assess for any significant difference between groups. Wilcoxon signed-rank test will be used to assess if there is any significant difference in matched questions. Free-text comment questions will be added to the questionnaire to further allow themes to develop, these will be reviewed independently by two researchers who will then critically review for emerging themes and collate responses within them.

10.0 Data Management

10.1 Data collection, handing and record keeping processes

Focus groups: After documentation of participants identifiable data in the enrolment log for the focus groups, anonymised demographic data (Years of practice, grade, ethnicity and department worked in) will be collected. To maintain participants anonymity when transcribing the focus group interviews individuals will be given participant identification number/code. This unique participant identification number/code will be used if themes/quotes are transcribed into a publication.

Questionnaire group: After the questionnaire has been formalised from the results of the focus groups and a detailed literature search, it will be sent out to relevant hospital trusts. Anonymised demographic data (years of practice, department you work in, type of hospital trust, grade, speciality) will be collected. 'Free text' boxes for participants to further explain their answers will be included for detailed thematic analysis. All responses to the questionnaire will be anonymised via completion through SurveyMonkey™.

All research staff are hospital employees (or have appropriate honorary contracts), and all medical staff on this study have dual clinical and research roles.

Electronic consent forms for involvement in the focus groups, enrolment log and PIS will be stored securely in the CI's institution, in the ISF.

10.2 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institutions and the regulatory authorities to permit study-related monitoring, audit, or inspection.

10.3 Essential Document Retention & Archiving

Archiving will be authorised by the Sponsor following submission of the end of study report.

Location and duration of record retention for:

- Essential documents: Patient case notes will be stored and maintained according to standard rules and procedures. Pathology results are stored and maintained according to standard procedures.
- Study data will be held for minimum of 10 years

Destruction of essential documents will require authorisation from the Sponsor.

11.0 Monitoring, Audits and Inspections

This study will be monitored and may be participant to monitoring and audit by University Hospital Southampton NHS Foundation Trust, under their remit as sponsor and other regulatory bodies to ensure adherence to ICH GCP, UK Policy Framework for Health and Social Care Research, applicable contracts/agreements and national regulations. All study related documents will be made available on request for monitoring and audit by UHS or relevant licensing bodies.

Based on the low risk of harm associated with this non-CTIMP study, no interim analysis, or Data Monitoring Committee is planned.

12.0 Ethics and Regulatory Considerations

The sponsor will ensure that the trial protocol, patient information sheet, consent form and submitted supporting documents have been approved by the appropriate regulatory body, Health Research Authority (HRA) and that local permission has been obtained prior to any subject recruitment.

All substantial amendments and non-substantial amendments (as determined by the sponsor) will not be implemented until HRA have provided the relevant authorisations. The NHS R&D departments will also be informed of any substantial amendments and non-substantial amendments. Relevant approvals must be obtained before any substantial amendment and non-substantial amendments may be implemented at sites.

All correspondence with the HRA will be retained in the Trial Master File and the Investigator Site File (maintained by the site).

Within 90 days after the end of the trial, the CI/Sponsor will ensure that the HRA are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply the Sponsor with a summary report of the clinical trial, which will then be submitted to relevant authorities within 1 year after the end of the trial.

All results will be published on a publicly accessible database.

12.1 Peer Review:

This protocol was independently reviewed by 2-3 different clinical academics within University Hospital Southampton NHS Trust who are not involved in the study itself.

13.0 Dissemination Policy

All publications arising from this work will acknowledge the organisations involved in the research - University of Southampton and University Hospital Southampton NHS Foundation Trust. The policy applies to all staff and students whose research outputs from pre-clinical and clinical research derive from their employment by the University and/or Trust, from research grants awarded to the University and/or Trust or otherwise from the use of University and/or Trust resources and facilities. The policy applies to all authors of publications, and not simply to principal authors or reprint authors. Citing both organisations on all papers covered by this policy acknowledges the success of each organisation resulting from working in partnership.

We intend for this protocol to be freely available on a public-facing website (e.g., ePrints Soton). The study shall be registered on clinicaltrials.gov.

PROTOCOL COMPLIANCE

The Investigator agrees to comply with the requirements of the Protocol and Good Clinical Practice. Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. it is not acceptable to enrol a subject if they do not meet the eligibility criteria or restrictions specified in the trial protocol.

Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol, which are found to frequently recur, are not acceptable and will require immediate action by the sponsor. Frequent non-compliances could potentially be classified as a serious breach.

Indemnity

The sponsor of the trial is University Hospital Southampton NHS Foundation Trust. For NHS sponsored research HSG (96) 48 reference no.2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

Data Protection

All investigators and study site staff will comply with the requirements of the Data Protection Regulation with regards to the collection, storage, processing and disclosure of personal information and will uphold the Regulation's core principles.

Definition of End of Study

The study end will be defined by the completion of all data collection undertaken as part of this study's data collection. The Chief Investigator will inform the HRA within 90 days of the study ending using the appropriate form.

14.0 References

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