Recording Antimicrobial Resistance during Death Certification in England

Study Acronym: AMR-DC

- **A**nti**m**icrobial **R**esistance in **D**eath **C**ertification

Version Control

Version:	Version 1.2
Date:	8/10/2024

Sponsor: Joint R&D Office for GOSH/ICH I UCL Great Ormond Street Institute of Child Health

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Collaborating Organisations/Sites:

British Society for Antimicrobial Chemotherapy (BSAC)

NHS England

UK Health Security Agency

London School of Hygiene and Tropical Medicine

Funder: UK Health Security Agency

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PROTOCOL VERSIONS

Version Stage	Versions No	Version Date	Protocol updated & finalised by;	Appendix No detail the reason(s) for the protocol update
Current	1.2	8/10/2024	Dr Louis Grandjean & Dr Ioannis Baltas	1. ISRCTN number added 2. Updated ICD-10 code categorisation 3. Addition of Diarrhoea and Typhoid, paratyphoid, and invasive non-typhoidal Salmonella infection syndromes 4. Updated infectious syndrome informative ranking 5. Updated study timeline and data collection end date.
Previous	1.1	25/05/2024	Dr Louis Grandjean & Dr Ioannis Baltas	1. CPMS ID added 2. REC and CAG reference No added 3. SGSS module clarification 4. Ascertainment factor adjustment added

				5. Adjustment in AMR pathogens of interest 6. Patient and Public Engagement and Involvement update 7. Garbage codes defined 8. ICD-10 codes updated 9. Updated age groups 10. Updated Supplementary table 2 11. Hierarchy of infectious syndrome added
Previous	1.0	6/2/2022	Dr Louis Grandjean & Dr Ioannis Baltas	N/A

DECLARATIONS

The undersigned confirm that the following protocol has been agreed and accepted and that the investigators agree to conduct the study in compliance with the approved protocol and will adhere to the UK Policy Framework for Health and Social Science Research (as amended thereafter), the University and Trust Data & Information Policy, Sponsor and other relevant SOPs and applicable University and Trust policies and legal frameworks.

We (investigators) agree to ensure that the confidential information contained in this document will not be used for any other purposes other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.
We (investigators) also confirm that an honest accurate and transparent account of the study will be given; and that any deviations from the study as planned in this protocol will be explained and reported accordingly.

Chief Investigator 1:

Signature: 

Date 8/10/2024
Print Name(in full): LOUIS GRANDJEAN
Position: Associate Professor, University College London

Chief Investigator 2:

Signature: Ioannis Baltas

Date 8/10/2024
Print Name(in full): IOANNIS BALTAS
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STUDY SUMMARY

Identifiers	
IRAS Number	340243
REC Reference No	24/NW/0084
Sponsor Reference No	23IF44
Other research reference number(s) (if applicable): CAG Reference Number: Data Protection Registration Number: Information Governance Advisory service CPMS ID ISRCTN registry No	 24/CAG/0050 Z6364106/2024/02/73 health research IG/01772 61354 - Antimicrobial Resistance in Death Certification ISRCTN96925141
Full (Scientific) title	Recording Antimicrobial Resistance during Death Certification in England
Health condition(s) or problem(s) studied	Antimicrobial resistance, Infection
Study Type i.e. Cohort etc	Retrospective cohort study
Target sample size	1.600.000 participants
STUDY TIMELINES	
Study Duration/length	12 months
Expected Start Date	01/05/2024
End of Study definition and anticipated date	Analysis of the data upon completion of the data collection, 5/6/2025.
FUNDING & Other	
Funding	UK Health Security Agency “University CARAA - University College London (Baltas and Lester) - Recording Antimicrobial Resistance during Death Certification in England (AMRDC)”
Other support	
STORAGE of SAMPLES (if applicable)	N/A
Human tissue samples	N/A.
Data collected / Storage	UCL Data Safe Haven
KEY STUDY CONTACTS	Full contact details including phone and email
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KEY ROLES AND RESPONSIBILITIES

SPONSOR: The sponsor is responsible for ensuring before a study begins that arrangements are in place for the research team to access resources and support to deliver the research as proposed and allocate responsibilities for the management, monitoring and reporting of the research. The Sponsor also has to be satisfied there is agreement on appropriate arrangements to record, report and review significant developments as the research proceeds, and approve any modifications to the design.

FUNDER: The funder is the entity that will provide the funds (financial support) for the conduction of the study. Funders are expected to provide assistance to any enquiry, audit or investigation related to the funded work.

CHIEF INVESTIGATOR (CI): The person who takes overall responsibility for the design, conduct and reporting of a study. If the study involves researchers at more than once site, the CI takes on the primary responsibility whether or not he/she is an investigator at any particular site.

The CI role is to complete and to ensure that all relevant regulatory approvals are in place before the study begins. Ensure arrangements are in place for good study conduct, robust monitoring and reporting, including prompt reporting of incidents, this includes putting in place adequate training for study staff to conduct the study as per the protocol and relevant standards.

The Chief Investigator is responsible for submission of annual reports as required. The Chief Investigator will notify the REC of the end of the study, including the reasons for the premature termination. Within one year after the end of study, the Chief Investigator will submit a final report with the results, including any publications/abstracts to the REC.

PRINCIPLE INVESTIGATOR (PI): Individually or as leader of the researchers at a site; ensuring that the study is conducted as per the approved study protocol, and report/notify the relevant parties – this includes the CI of any breaches or incidents related to the study.

Table of Contents

1. Introduction

1.1 Glossary of Abbreviations

AMR	Antimicrobial Resistance
BL/BLI	Beta-lactam/beta-lactamase inhibitor
CI	Confidence Interval
CLSI	Clinical and Laboratory Standards Institute
CSF	Cerebrospinal Fluid
ESBL	Extended Spectrum Beta-Lactamase
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	Food and Drug Administration
HES	Hospital Episode Statistics
HIC	High Income Countries
ICD	International Classification of Diseases
ICU	Intensive Care Unit
IRAS	Integrated Research Application System
KPC	Klebsiella pneumoniae carbapenemase
LMIC	Low- or Middle-Income Country
MCCD	Medical Certificate of Cause of Death
MCD	Multiple Causes of Death
MDR	Multi-drug resistant
MIC	Minimum Inhibitory Concentration
NDM	New Delhi metallo-beta-lactamase
NHS	National Health Service
OXA-48	Oxacillinase 48
RCPath	Royal College of Pathologists
REC	Research Ethics Committee
SGSS	Second Generation Surveillance System
UCOD	Underlying Cause of Death
UKHSA	UK Health Security Agency
WGS	Whole genome sequencing
WHO	World Health Organisation

1.2 Key Definitions

Antimicrobials: medicines used to prevent and treat infection in humans, animals and plants, includes antibacterial, antiviral, antifungal, and antiparasitic drugs.

Antimicrobial resistance: when bacteria, viruses, fungi and parasites no longer respond to antimicrobial medicines. As a result of drug resistance, antibiotics and other antimicrobial medicines become ineffective and infections become difficult or impossible to treat, increasing the risk of disease spread, severe illness, disability, and death.

Medical certificate of cause of death: a permanent legal record completed by a doctor, that allows registration of a person's death. It states the deceased's name and age, as well as how and where the person died. In England, the conditions that directly caused the person's death are recorded in sections Ia, Ib and Ic (the most immediate cause first in Ia), while other contributing conditions are listed in section II.

International Classification of Diseases: a coding system published by the World Health Organisation for the purposes of disease classification, currently in its 11th version (since 01/01/2022). It is used worldwide and allows standardised epidemiological monitoring of mortality and morbidity statistics.

Hospital episode statistics: a curated database held by NHS England containing details about admissions, outpatient appointments and historical Accident and Emergency attendances at NHS hospitals in England.

Multiple Causes of Death: a method of recording the cause of death of a person by including not only the underlying cause but also the immediate cause of death and all other intermediate and contributory conditions listed on the medical certificate of cause of death.

Medical examiner: senior medical doctors based in acute NHS Trusts who are contracted to provide independent scrutiny of the causes of death, outside their usual clinical duties. In England, the role of medical examiners is to agree the proposed cause of death and the overall accuracy of the medical certificate of cause of death (MCCD)

with the doctor completing it. They are trained in the legal and clinical elements of death certification processes.

NHS Trust: an organisational unit within the National Health Services of England and Wales, generally serving either a geographical area or a specialised function. NHS Trust can consist of one or multiple individual hospitals.

Underlying Cause of Death: a method of recording the cause of death of a person that records only the disease or injury, as recorded on the medical certificate of cause of death, that initiated the series of events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury.

1.3 Abstract

Background and Rationale: AMR is a leading cause of mortality worldwide. Estimating the total number of deaths associated with AMR is important yet challenging, as modelling approaches have significant limitations. The UK government is currently implementing changes to the Medical Examiners' System in order to facilitate improved recording of AMR during death certification. Changes are expected to be implemented in April 2024. Towards this purpose, recent guidance was published from the RCPath, including a list of important AMR pathogens that ought to be recorded on MCCDs. Recording AMR-associated deaths directly by linking patient-level data, including death certification and microbiological data is an important approach for accurately estimating AMR-associated mortality. Despite that, many cases may be missed during routine clinical practise.

Project Aims:

1) Describe the burden and trend of AMR-associated mortality in England in the years 2021 through to 2023.

2) Establish a pathway for public health authorities for calculating AMR-associated deaths in England using routinely collected data.

Project Objectives:

1) Calculate the total number of deaths in England in the years 2021, 2022 and 2023, in which death was associated with AMR.
2) Describe the monthly trend of AMR-associated deaths in England across 2021, 2022 and 2023.
3) Calculate the percentage of all deaths that can be attributed to AMR.
4) Calculate the percentage of deaths from infection that can be attributed to AMR.
5) Describe which pathogens, pathogen-drug combinations and resistance mechanisms are responsible for the largest number of deaths in England.
6) Describe the cohort of patients with AMR-associated deaths with regards to demographic and clinical characteristics and compare them with patients who die due to drug-sensitive infections.
7) Calculate the percentage of deaths in which an AMR pathogen of interest was isolated, yet infection was not recorded as a cause of death on the MCCD, and describe this cohort of patients.

Target Population: All patients who had their death registered in England between 01/01/2021 and 31/12/2023.

Project Design and Methods: This will be a retrospective observational cohort study. Eligible patients will be identified through the Civil Registrations of Death database provided by NHS England and will be linked to the HES database, also held by NHS England, to obtain additional clinical metadata. Pseudonymised cases will be subsequently linked to the SGSS database (AMR module) held by UKHSA in order to detect clinical samples with AMR pathogens of interest within 28 days of the patient's death. Anonymised results will be analysed using a standardized pathway to determine whether each death was AMR-associated. The rate and total number of deaths associated with AMR in this cohort, the most important pathogens, pathogen drug-combinations and resistance mechanisms will be described.

Project Assessment/Evaluation: Findings will be published in peer reviewed journals and presented in national and international meetings.

Project Outcomes: To the best of our knowledge, this project will be the first to estimate the total number of deaths associated with AMR in England by linking MCCDs to microbiological results. This methodology uses patient level-data and therefore is a lot more likely to produce an accurate estimate of AMR-associated deaths compared to pure modelling studies. It will also act as a benchmark for the new death certification process for AMR, allowing to assess how well AMR-associated deaths are recorded during routine clinical practise.

1.4 Background

AMR is a leading cause of mortality worldwide. It is estimated to have caused 1.27 million deaths in 2019 and is projected to cause 10 million deaths every year by 2050.[1,2] Precise estimation of the mortality burden of AMR is important, as it raises awareness regarding the magnitude of the problem among relevant stakeholders, including governments and the public. It also allows accurate epidemiological monitoring of drug-resistant infections and correct allocation of resources to address the infections with the highest burden of disease.

Despite established national vital statistic registries in most countries in 2023, especially HICs, knowing how many people die of antibiotic-resistant infections is difficult to determine. The challenges arise from multiple sources: infections, including drug-sensitive infections, are rarely recorded as the Underlying Cause of Death (UCOD), which is the WHO's preferred approach for reporting causes of death, as physicians often prioritise chronic conditions.[3] This can be circumvented by using the Multiple Causes of Death (MCD) approach, in which the underlying cause, but also the immediate cause of death and all other intermediate and contributory conditions listed on the medical certificate of cause of death are reported; yet, this is again limited by the fact that AMR is rarely recorded on the medical certificate of cause of death (MCCD).[4] Up until 2022, even if AMR was recorded on the MCCD, there were no ICD-10 codes to capture this information for national reporting.[5] This has now been amended in the ICD-11 version, which has not been widely adopted. Additionally, general physician awareness to record resistant organisms on the death certificate remains a significant hurdle. Challenges are further compounded by the lack of availability of microbiological testing in many settings, especially LMICs, to determine if a death was attributable to AMR.[6] Due to these hurdles, to our knowledge, no studies to date have reported AMR-associated deaths by linking death certification and microbiological data. In contrast, studies reporting estimates of AMR-associated deaths, including the previously mentioned impactful studies, rely on modelling to draw their conclusions.[1,2] Yet, this is limited by multiple assumptions made and lack of high-quality underlying data to inform models, including total numbers of infections and precise case-fatality ratios.[3]

The importance of accurately counting AMR-associated deaths has been recently recognised by the UK government and the National Medical Examiners' Office, who published guidance on correct AMR documentation on the MCCD.[7] This, with the aid of the new ICD-11 coding, is expected to improve recording of AMR on MCCDs. It should be noted that this process will rarely be led by infectious diseases and microbiology physicians during routine practice, although consultation will be available. For this reason, many AMR-associated deaths may still be missed.

In summary, AMR-associated deaths are hard to estimate due to a series of challenges, including limitations in existing reporting systems to record AMR at the time of death, limitations in modelling due to lack of reliable data, reduced access to microbiological testing to detect AMR, and lack of awareness among physicians on the impact of AMR in infection-related deaths. In England, there have been some recent legislative changes aiming to aid reporting of AMR in MCCDs, but underreporting during routine practise is still to be expected. For this reason, we designed this study to accurately record the numbers of AMR-associated deaths in England over a period of three years and set a benchmark for the new process of AMR-death certification starting in the country.

2. Hypotheses

1) That it is possible to calculate AMR-associated deaths by linking death certification and patient-level microbiological data.

2) That AMR-associated mortality has been increasing in England during the study period.

3) That AMR was associated with a significant number of deaths (>2% of total deaths) in England in 2021-2023.

4) That a significant proportion of deaths (>10%) due to infection in England in 2021, 2022 and 2023 were AMR-associated.

5) That ESBLs were the AMR resistance mechanism with the highest number of AMR-associated deaths in England during the study period.

6) That most AMR-associated deaths (>90%) occur in hospital, disproportionately affect patients in Intensive Care and patients under Haematology and Oncology.

7) That patients recording AMR-associated deaths have longer hospital length of stays, are more likely to be admitted to Intensive Care and require more prolonged organ support.

3. Study Lead, Study Setting and Collaborating Sites

Study Lead: The Department of Infection, Immunity and Inflammation, Great Ormond Street Institute of Child Health in University College London will act as the study lead and sponsor. Collaborating organisations will include the British Society for Antimicrobial Chemotherapy, NHS England, the UK Health Security Agency and the London School of Hygiene and Tropical Medicine.

4. Lay Summary

Antimicrobial resistance refers to when bacteria, viruses, fungi and parasites (bugs) no longer respond to antibiotic medicines. It is usually caused by prolonged and repeated exposure of bugs to antibiotics, in people, animals or the environment, which helps bugs eventually build defence mechanisms against them. These bugs can then spread via contact from person to person, causing resistant infections to people who have not had antibiotics before. For this reason, previously effective treatments stop working due to antimicrobial resistance worldwide. Research has shown that infections from antibiotic resistant bugs are more likely to lead to death, disability, and additional stay in hospital. It has also been estimated that, by 2050, 10 million deaths a year will be caused by antimicrobial resistance.

Despite the importance of antimicrobial resistance, which has been characterised as a global health emergency by the World Health Organisation, we have limited information about how many people die every year due to infections resistant to antibiotics. This is because of a variety of factors. For example, studies have shown that doctors are more likely to record chronic health problems like cancer in the death certificate as the primary cause of death, and the contribution of infection is often underestimated. Another problem is that in order to find antibiotic resistant bugs, cultures from the patient need to be taken, which is not always performed. This leads to underestimation of true numbers of antibiotic resistant infections. Yet, knowing exactly how many people die due to antimicrobial resistance is important, as it drives political and public awareness about the problem, highlighting the need for better treatments.

Very few previous studies have tried to estimate the true numbers of deaths due to antibiotic resistant infections. They have primarily used a technique called modelling to do so. Modelling uses math to estimate the numbers of deaths, based on how groups of patients with antibiotic sensitive and antibiotic resistant infections behave, as well as total numbers of infections. Because modelling doesn’t look at individual patient cases though, it can lead to erroneous results and underestimation of the problem.

In this study, we will attempt for the first time to calculate the total number of deaths caused by antibiotic resistant infections in England in 2021, 2022 and 2023. We aim to do that by anonymously linking the cause of death of each patient as documented on the death certificate with the bugs they were positive for in cultures and specimens up to 28 days before the date of death. Every patient who died in England in 2021, 2022 and 2023 will be included in the study but their data will be collected in a way that will not allow them to be identified. Participants who expressed their wish for their data not to be used for research purposes before they died will be excluded. We believe that with this approach

we will get more accurate data on the total number of people in England, in whom antimicrobial resistance contributed to their death.

5. Study Methodology

5.1 Ethics and governance:

Dedicated Independent Health Research Authority REC approval through IRAS will be obtained for this study. Eligible patients will be identified through the NHS England Civil Registration of Death database. Data linkage will be performed to the NHS England HES database and the UKHSA SGSS microbiology database. No identifiable patient data will be accessed by the study investigators, but the application will seek support from the Confidentiality Advisory Group (CAG) under Section 251 (Precedent Set Criteria 4 pathway) to allow cohort generation, linkage and dissemination of the required datasets by NHSE and UKHSA. Patients under the National Data Opt Out (DOO) will be excluded (estimated at 5.4%). A proposed data flowchart is shown in Figure 1. Identifiable patient field in each dataset (Civil Registration of Death database, HES and SGSS database) will be pseudonymised by the respective data holders (NHSE and UKHSA) using the same code. The pseudonymised datasets will then be linked using the NHS number. Data minimisation will be applied as detailed below. A final fully anonymised dataset (Section 251 exit strategy) will then be made by removing all pseudonymised patient identifiable data (date of birth, date of death, postcode, sample collection date, NHS number) and will be shared with the study investigators via secure encrypted email (AES-256 encryption with password). These will be stored and handled in the UCL Data Safe Haven. The study investigators will not have the ability to de-anonymize the data. Since the study will only use fully anonymised data, no consent from patients or family members will be obtained. This would have also been impracticable due to the nature of the study (deceased patients). The Next of Kin could not have given consent in this situation either, unless they were the Legal Personal Representative. Anonymised data will be held by the study sponsor for three years in the UCL Data Safe Haven. No human tissue will be stored or processed as part of this research. No paper records will be produced from this study. All electronic data transfers will be encrypted.

Data minimisation: The following data minimisation techniques will be used: Age groups will be collected instead of age in years, ICD-10 codes for cause of death instead of free-text fields, month and year of death instead of date of death, days from sample collection to date of death instead of sample date, NHS England region of death instead of postcode of place of death.

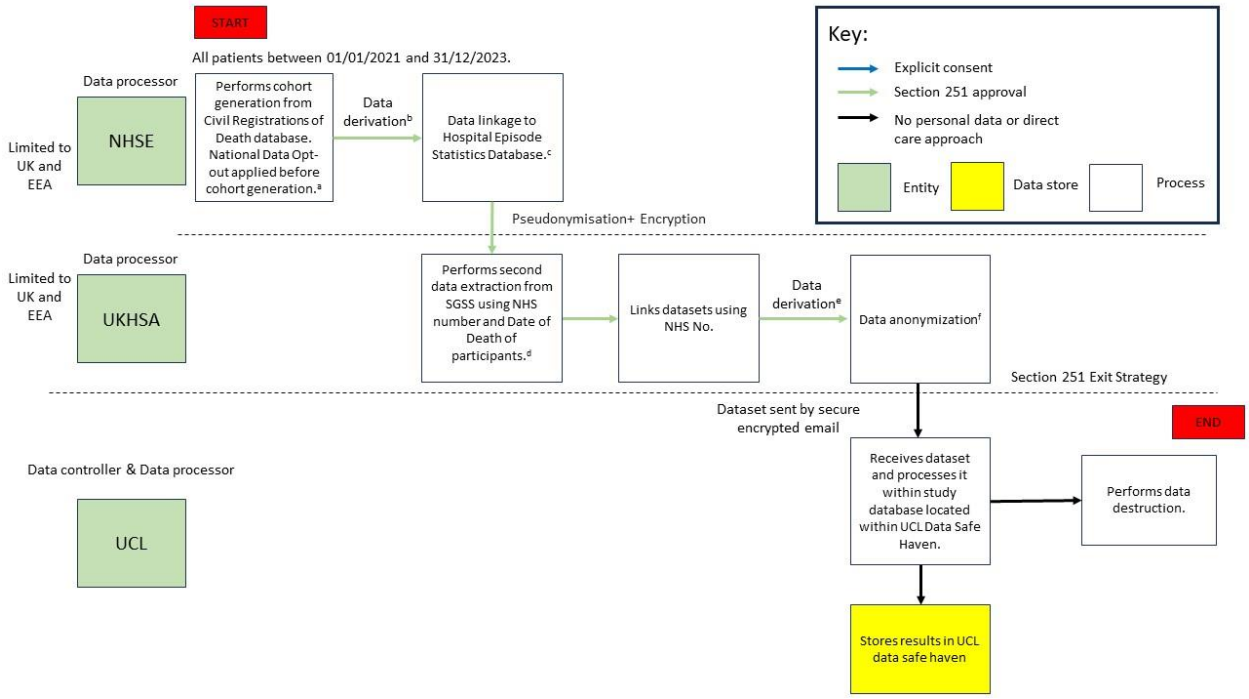


Figure 1 Data Flowchart

[a]Data collected: NHS Number, Age, Sex, Postcode, Place of Death Postcode, Causes of death, Date of death.
[b]Age group from age, Decile of Multiple Index of Deprivation from Postcode, NHS region from Place of Death Postcode
[c]Data collected: Ethnicity, death as inpatient or discharge to hospice, mode of admission, duration of final admission, number of specialties during final admission, specialties during final admission, ICU admission during final admission, duration of ICU admission, number of life-support days during final admission, ICD-10 diagnoses during final admission.
[d]Data collected: sample date, sample type, pathogen identity, resistance profile, any additional tests performed, phenotypic or molecular.
[e]Days between date of death and sample date, month and year of death from date of death.
[f]Removal of NHS number, Age, Postcode, Place of Death Postcode, Date of death, sample date.

5.2 Study design

This will be a retrospective observational cohort in England in the years 2021-2023.

5.3 Study population

All patients who had their death registered in England between 01/01/2021 and 31/12/2023 will be included in this study. Only patients who had expressed the wish for their data not to be used for research purposes under the DOO will be excluded. Each participant will be given a unique study identification number.

5.4 Variables

The following variables will be collected for each participant:

- Age (in the following age groups: (0–6, 7–27, 28-364 [days], 1–4, 5–9, 10–14, 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, 85–89, 90–94, 95+ [years]).
- Sex (Male or Female or Other or Not known or not stated)
- Ethnicity (White, Asian/Asian English, Black/African/Caribbean/Black British, Mixed / multiple ethnic groups, Any other ethnic group, Not known or not stated).
- The decile of the Multiple Index of Deprivation.
- Cause of death as detailed in the MCCD (sections Ia, Ib, Ic, II) using ICD-10 (or ICD-PM) codes.
- The month and year of death.
- The NHS region where the death was recorded (East of England, London, West Midlands, East Midlands, North East, Yorkshire and Humber, North West, South East, South West).
- Results of all microbiological investigations recorded in SGSS (AMR module) within 28 days of the date of death (including days between sample collection date and date of death, sample type, pathogen identity, resistance profile, any additional tests performed, phenotypic or molecular).

- Results from the HES database (death as inpatient or discharge to hospice, mode of admission, duration of final admission, number of specialties during final admission, specialties during final admission, ICU admission during final admission, duration of ICU admission, number of life-support days during final admission, ICD-10 diagnoses during final admission).

5.5 The AMR pathogens of interest

AMR is a microbiological diagnosis. Therefore, only patients who isolated important AMR pathogens in clinical samples for suspected infection (not screening samples) will be eligible to be considered to have suffered an AMR-associated death for the purposes of this study.

The pathogens of interest for this study will be based on the ones suggested by the recent RCPath document "Recording antimicrobial resistance on the Medical Certificate of Cause of Death".[7] A wider definition for Enterobacterales (including resistant isolates to BL/BLI combinations and aminoglycosides but excluding 4th and 5th generation cephalosporin resistant isolates) and *Pseudomonas aeruginosa* (including Multi-drug Resistant (MDR) phenotype and carbapenem resistant isolates) will be used. This was decided because BL/BLIs and aminoglycosides constitute a significant proportion of hospital prescribing for suspected and proven infection in England.[8] For this reason, resistance to BL/BLIs and aminoglycosides in Enterobacterales is often likely to lead to delayed *in vitro* effective treatment, which is strongly linked to increased likelihood of death, and thus AMR-associated mortality.[9] On the contrary, 4th and 5th generation cephalosporins are rarely used clinically in the UK for the empirical treatment of Gram-negative infections.[8] Additionally, resistant isolates are expected to be 3rd generation cephalosporin resistant as well, and therefore will be captured. This categorisation is in line with the methodology in the GRAM study and categorisations used in the ESPAUR report.[10]

For *Pseudomonas aeruginosa*, the RCPath definition of resistance (suggesting only carbapenemase producing carbapenem-resistant isolates were significant) was deemed

to be too narrow, as a very small percentage of *Pseudomonas aeruginosa* in England produce carbapenemases.[8] Despite that, resistance to clinically important antimicrobials that leads to delays in treatment is often mediated by different resistance mechanisms. For this reason, the wider definition of MDR *Pseudomonas aeruginosa* (not susceptible to at least one antibiotic in at least three antibiotic classes for which P. aeruginosa susceptibility is generally expected: antipseudomonal penicillins, antipseudomonal cephalosporins, fluoroquinolones, aminoglycosides, carbapenems, monobactams and colistin) was chosen.[11] Carbapenem-resistant *Pseudomonas aeruginosa* was chosen as it a WHO priority AMR pathogen and number of infections is a performance indicator for the 2024-2029 UK AMR National Action Plan.[12]

For *Mycobacterium tuberculosis*, the RCPath definition of resistance included any resistance to isoniazid, rifampicin, fluroquinolones, aminoglycosides, linezolid or bedaquiline. Yet, resistance to second line agents (fluroquinolones, aminoglycosides, linezolid or bedaquiline) is unlikely to be significant in strains susceptible to first line agents (isoniazid and rifampicin), which would be treated with standard quadruple therapy. Therefore, a narrower definition included isoniazid or rifampicin resistant *Mycobacterium tuberculosis* was chosen.

For *Candida spp*, amphoteric B was added to the list of drugs due to its widespread use in empirical treatment of invasive fungal disease in the UK.[8] Other azoles apart from fluconazole were excluded to reflect prescribing practises in England for the empirical management of suspected *Candida spp* infection. Other azoles are rarely used empirically in the initial stages of infection where susceptibility results are not known (NHS England and Dr Neil Stone, personal communication). Therefore, resistance to these agents would be unlikely to lead to empirical treatment failure and delay in treatment associated with AMR mortality.

Pathogens of interest will need to be isolated in culture of appropriate clinical specimens taken for the diagnosis of active infection (not screening samples). Positive results of validated molecular tests for each pathogen of interest will also be recorded even in the

absence of confirmatory microbiological cultures although these are not frequently captured by SGSS.[8]

The hierarchical approach in classifying resistance to different antimicrobial classes was adopted from the 2022-2023 ESPAUR report[8] and was selected to avoid the conceptually troublesome situation where the total number of deaths from all antimicrobial categories counted is greater than the number of participants who died.

Gram-positive bacteria:

1. Methicillin-resistant *Staphylococcus aureus*[a]
2. Vancomycin-resistant enterococci[b]
3. Penicillin-tolerant or Penicillin-resistant *Streptococcus pneumoniae*[c]
4. Macrolide-resistant *Streptococcus pneumoniae*[d]

[a]defined as *Staphylococcus aureus* with Cefoxitin MIC >4mg/L or Cefoxitin zone diameter <22mm or positive molecular test for mecA or mecC genes).
[b]defined as *Enterococcus spp* with Vancomycin MIC >4mg/L or Vancomycin zone diameter <12mm or positive molecular test for VanA, VanB, VanC genes.
[c]defined as *Streptococcus pneumoniae* with Benzylpenicillin MIC >0.06mg/L and *Streptococcus pneumoniae* with Benzylpenicillin MIC >2mg//L respectively.
[d]defined as *Streptococcus pneumoniae* with an Erythromycin, Clarithromycin and Azithromycin MIC >0.25 or Erythromycin disc diameter <22mm.

Gram-negative bacteria:

1. Enterobacterales resistant to the following antibiotic classes:
    - carbapenems[e]
    - antipseudomonal penicillin/beta-lactamase inhibitor[f] (excluding isolates also resistant to carbapenems)

- third-generation cephalosporins[g] (excluding isolates also resistant to carbapenems and antipseudomonal penicillin/beta-lactamase inhibitors)
- aminoglycosides[h] (excluding isolates also resistant to carbapenems and/or antipseudomonal penicillin/beta-lactamase inhibitors and/or third-generation cephalosporins)
- fluoroquinolones[i] (excluding isolates also resistant to carbapenems and/or antipseudomonal penicillin/beta-lactamase inhibitor and/or third-generation cephalosporins and/or aminoglycosides)
- beta lactam/beta-lactamase inhibitor[j] (excluding isolates also resistant to carbapenems and/or antipseudomonal penicillin/beta-lactamase inhibitorand/or third-generation cephalosporins and/or aminoglycosides and/or fluroquinolones)

[e]defined as Enterobacterales with Meropenem MIC >8mg/L and/or Meropenem zone diameter <16mm OR Imipenem MIC >4mg/L and/or Imipenem zone diameter <19mm OR Ertapenem MIC >0.5mg/L and/or Ertapenem zone diameter <25mm.

[f]defined as Enterobacterales with Piperacillin-tazobactam MIC >8 and/or Piperacillin-tazobactam zone diameter <20mm.

[g]defined as Enterobacterales with Ceftriaxone MIC >2mg/L and/or Ceftriaxone zone diameter <22mm OR Cefotaxime MIC >2mg/L and/or Cefotaxime zone diameter <17mm OR Ceftazidime MIC >4mg/L and/or Ceftazidime zone diameter <19mm.

[h]defined as Enterobacterales with Amikacin MIC >8mg/L and/or Amikacin zone diameter <18mm OR Gentamicin MIC 2mg/L and/or Gentamicin zone diameter <17mm.

[i]defined as Enterobacterales with Ciprofloxacin MIC >0.5mg/L and/or Ciprofloxacin zone diameter <22mm OR Levofloxacin MIC >1mg/L and/or Levofloxacin zone diameter <19mm.

[j]defined as Enterobacterales with Amoxicillin-clavulanic acid MIC >8mg/L and/or Amoxicillin-clavulanic acid zone diameter <19mm. This excludes Enterobacterales resistant to Amoxicillin-clavulanic acid due to an expected phenotype according to EUCAST (*Citrobacter freundii, Enterobacter cloacae complex, Hafnia alvei, Klebsiella*

aerogenes, Morganella morganii, Plesiomonas shigelloides, Providencia rettgei, Providencia stuartii, Serratia marcescens, Yersinia enterocolitica).[13]

For *Shigella spp* and *Salmonella spp* only resistance to carbapenems, third generation cephalosporins and fluroquinolones will be taken into account.

2. *Acinetobacter spp* resistant to the following antibiotic classes:

   - carbapenems[k]
   - fluroquinolones[l] (excluding isolates also resistant to carbapenems)
   - aminoglycosides[m] (excluding isolates also resistant to carbapenem and/or fluroquinolones)

[k]defined as *Acinetobacter spp* with Meropenem MIC >8mg/L and/or Meropenem zone diameter <15mm **OR** Imipenem MIC >4mg/L and/or Imipenem zone diameter <21mm).
ldefined as *Acinetobacter spp* with Ciprofloxacin MIC >1mg/L and/or Ciprofloxacin zone diameter <21mm OR Levofloxacin MIC >1mg/L and/or Levofloxacin zone diameter <20mm.
[m]defined as *Acinetobacter spp* with Amikacin MIC >8mg/L and/or Amikacin zone diameter <19mm OR Gentamicin MIC 4mg/L and/or Gentamicin zone diameter <17mm

3. *Pseudomonas aeruginosa* resistant to the following antibiotic classes:

- Carbapenems[n]
- three out of the following antimicrobial classes (if not resistant to carbapenems)
  - Antipseudomonal penicillins[o]
  - Antipseudomonal cephalosporins[p]
  - Fluoroquinolones[q]
  - Aminoglycosides[r]
  - Monobactams[s]

- Colistin[t]

[n]defined as *Pseudomonas aeruginosa* with Meropenem MIC >8mg/L and/or Meropenem zone diameter <14mm **OR** Imipenem MIC >4mg/L and/or Imipenem zone diameter <20mm).

[o]defined as *Pseudomonas aeruginosa* with Piperacillin-tazobactam MIC >16mg/L and/or Piperacillin-Tazobactam zone diameter <18mm.

[p]defined as *Pseudomonas aeruginosa* with Ceftazidime MIC >8mg/L and/or Ceftazidime zone diameter <17mm **OR** Cefepime MIC >8mg/L and/or Cefepime zone diameter <22mm

[q]defined as *Pseudomonas aeruginosa* with Ciprofloxacin MIC >0.5mg/L and/or Ciprofloxacin zone diameter <26mm **OR** Levofloxacin MIC >2mg/L and/or Levofloxacin zone diameter <18mm).

[r]defined as *Pseudomonas aeruginosa* with Amikacin MIC >16mg/L and/or Amikacin zone diameter <15mm **OR** Tobramycin MIC >2mg/L and/or Tobramycin zone diameter <18mm).

[s]defined as *Pseudomonas aeruginosa* with Aztreonam MIC >16mg/L and/or Aztreonam zone diameter <18mm.

[t]defined as *Pseudomonas aeruginosa* with Colistin MIC >4mg/L.

Other bacteria:

Mycobacterium tuberculosis resistant to one or both of the following agents:

- Isoniazid
- Rifampicin

All Mycobacterial resistance testing in England is performed by the National Mycobacterium Reference Service using both genotypic and phenotypic methods.[14] First line testing includes Whole Genome Sequencing (WGS)-based sensitivities for Isoniazid,

Rifampicin, Ethambutol, Pyrazinamide, Quinolones, Streptomycin and Aminoglycosides, as well as phenotypic testing for Isoniazid, Rifampicin and Ethambutol. Second line phenotypic testing for rifampicin-resistant strain includes Moxifloxacin, Levofloxacin, Amikacin, Kanamycin, Prothionamide, Capreomycin, Linezolid. Third line testing includes Delamanid, Clofazimine and Bedaquiline performed in reference laboratory in Italy.[14]

Patients without positive cultures to allow full susceptibility profiling but positive molecular tests for *Mycobacterium tuberculosis* suggesting rifampicin resistance (e.g. rpoB mutation) will also be included.

Fungi

Candida species (including *Candida auris*) resistant to ≥1 agent in one or more of the following drug classes:

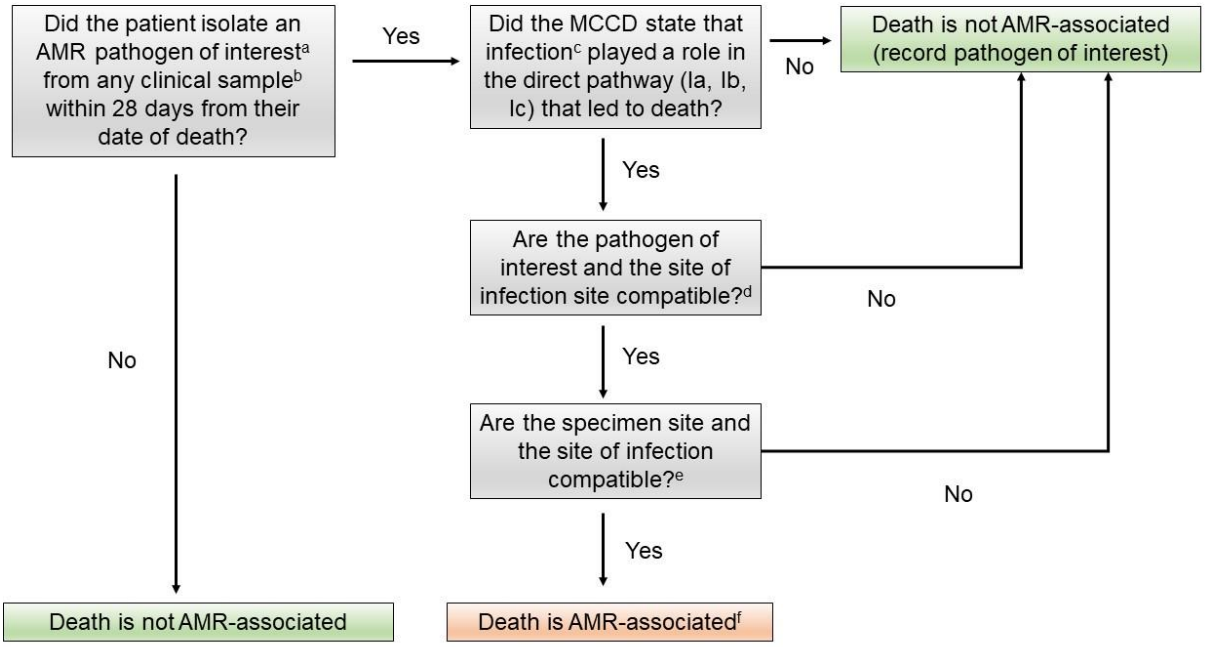
- Amphotericin B
- Echinocandins (Anidulafungin, Caspofungin, Micafungin) - excluding isolates also resistant to amphotericin B
- Azoles (Fluconazole only) - excluding isolates also resistant to amphotericin B and echinocandins.

For *Candida spp*, if interpretation of MICs has been performed by the reporting laboratory, resistance to the agents will be recorded as determined at the time of testing. If MIC ranges are provided only, the resistance profile will be determined by the study investigators according to EUCAST and CLSI guidance.[15,16] In England, during the study period, laboratories use the EUCAST breakpoints for anti-fungal susceptibility testing.[16] If no breakpoints are available, CLSI breakpoints are used.[15] For *Candida auris*, the tentative breakpoints suggested by the CDC will be used as below.[17]

Antifungal agent	Tentative MIC Breakpoints (µg/mL)	Comment
Fluconazole	≥32	
Amphotericin B	≥2	
Anidulafungin	≥ 4	
Caspofungin	≥ 2	
Micafungin	≥ 4	

5.6 Data collection

Whether each participant suffered an AMR-associated death will be determined using a standardized approach according to the following flowchart.



[a]The pathogens of interest for this study will be based on the ones suggested by the recent RCPath document "Recording antimicrobial resistance on the Medical Certificate of Cause of Death"[7], with deviations as described in section 5.5 of the study protocol.

[b]Only includes samples obtained for the diagnosis of active infection (exclude screening samples). Includes positive results of cultures or validated molecular tests for each pathogen of interest.

[c]Includes all infectious syndromes and/or sequelae of infection e.g. sepsis as defined by ICD-10 codes (See supplementary Table 1 in the Appendix).[5]

[d]Compatible combinations of pathogens of interest and sites of infection are shown in Supplementary table 2 in the Appendix.

[e]The specimen must be taken from a site that supports the suggested site of infection. For example, if the site of infection is pneumonia, a sputum sample or blood culture growing MRSA would satisfy this criterion, while a urine culture growing the exact same pathogen would not. An exhaustive table is shown in Supplementary Table 3.

[f]If more than one pathogen of interest is isolated and fulfil the criteria necessary to record an AMR-associated death, they will be considered equally responsible for the participants death. Each pathogen will be assigned the number of deaths for this participant according to the following formula: Associated deaths count = 1/the total number of pathogens of interest that fulfil the criteria necessary to record an AMR-associated death for this participant. This is to avoid the conceptually troublesome situation where the total number of deaths counted is greater than the number of participants who died.

If multiple infectious syndromes are present on the death certificate, the informative ranking in Supplementary Table 4 will be applied when counting the total number of infections to avoid double-counting and the troublesome situation where the total number of deaths counted is greater than the number of participants who died, as previously described.[1]

With local permissions, an audit in University College London NHS Foundation Trust was performed before the launch of this study to test the robustness of the proposed work flowchart using patient level-data for all inpatient deaths in 2022 (Figure 2). No issues with the performance of the flowchart were identified. Deaths determined as AMR-associated by the flowchart correlated well with the assessment of two expert infectious diseases and microbiology physicians, who both assessed the cases independently with

access to the entire medical record. In summary, 3.3% (25/758) of all deaths were deemed to be AMR-associated according to the flowchart, while 12.7% (96/758) of all patients had an AMR pathogen of interest within 28 days of their date of death, requiring assessment for association. Note the reported numbers are likely over-estimating AMR-associated mortality compared to the proposed study cohort as they examine inpatient deaths only from a tertiary centre with a large haematology and bone marrow transplant population.

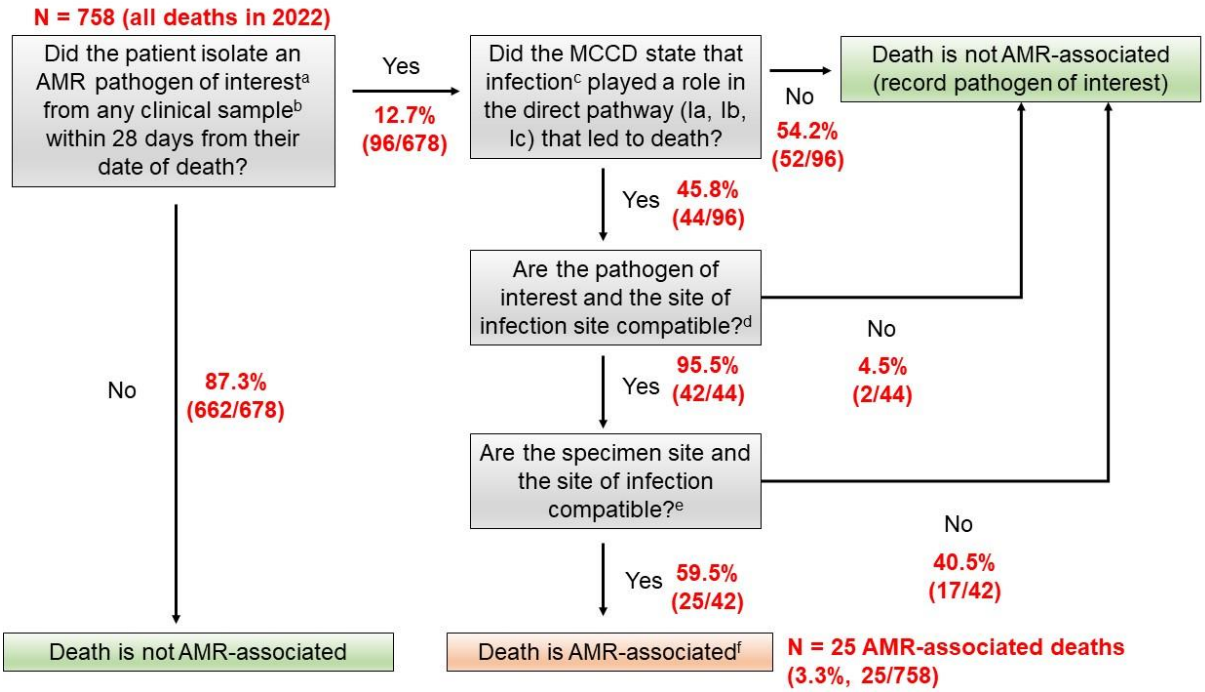


Figure 2 Results from a local UCLH audit using the same methodology as the proposed study.

5.7 Sample size

There were 549,409 and 540,333 deaths in England in 2021 and 2022 respectively according to the Office of National Statistics.[18] Similar numbers are expected for 2023 (e.g. 540,000). Therefore the total sample size of this study will be approximately 1,600,000 participants. This will include inpatient and outpatient deaths, which is a significant strength. Most AMR-associated deaths (approximately 95%) are expected to have happened in hospital.[19]

The Microbe database[20] estimated that in 2019 in the United Kingdom there were 7,125 AMR-associated deaths (1.34% of all deaths N = 530,841 total deaths in England in 2019, Table 1) from the pathogens of interest using a pure modelling approach. We will attempt to confirm this estimation by calculating AMR-associated deaths from MCCDs. It should be noted that direct comparison might yield different results for the following reasons:

1) temporal mismatch (2019 versus 2022)
2) geographical mismatch (10% more population in the UK compared to England-Wales alone)
3) wider AMR-associated death definition (including resistance to more antimicrobials e.g. co-trimoxazole for Enterobacterales)
4) non-inclusion of deaths from *Candida spp*

Adjusting for these small differences, if modelling calculations used for the database are true,[1] we expect to find approximately 5,744 AMR-associated deaths in our cohort each year on average, and in total 17,232 AMR-associated deaths (Table 2).

Table 1

AMR pathogen of interest	Estimated deaths in 2019 according to the Microbe database[20]
Escherichia coli	2,578
Staphylococcus aureus	1,371
Enterococcus faecium	821
Klebsiella pneumoniae	757
Streptococcus pneumoniae	448
Pseudomonas aeruginosa	442
Acinetobacter baumannii	369
Enterococcus faecalis	262
Citrobacter species	45
Serratia species	21
Mycobacterium tuberculosis	12

Total	7,125

Table 2

Sample size estimation steps	Number of deaths
Initial estimation - Estimated deaths in 2019 according to the Microbe database[20]	7,125
Step 1: temporal mismatch 2019 versus 2022 (assuming 7% increase per year)[2]	8,728
Step 2: Population size difference (UK 67.3 millions compared to England-Wales alone 59.7 millions)	7,742
Step 3: Wider AMR-associated death definition (69.1% of pathogen-drug combinations included)[1]	5350
Step 4: Deaths per year from resistant Candida species added[21]	394
Total	5,744

5.8 Data analysis

Analysis of results will be performed in R.[22] Categorical variables will be expressed as percentages with 95% CIs, continuous variables will be expressed as means or medians with 95% CIs. 95% CIs will be calculated using 10,000 bootstrap samples. Univariable comparisons of proportions will be performed using the Chi-squared test. The following results will be produced.

- The total number and percentage of AMR-associated deaths in 2021, 2022 and 2023, including the monthly trend of totals numbers. Linear regression and time series analysis will be used to assess for statistically significant change in the number of AMR-associated deaths over time.
- The total number and percentage of AMR-associated deaths for each site of infection, AMR pathogen of interest, pathogen-drug combination, and resistance mechanism.
- UCOD and MCDs groupings percentages for the entire study cohort. UCOD and MCDs will be determined from MCCDs as per WHO methodology using the Office of National Statistics ICD-10 groupings with the addition of COVID-19

under codes U07.1 and U07.2.[23,24] Garbage codes, if identified, will be redistributed to appropriate targets as previously described.[25]

- The total number and percentage of UCOD and MCDs that were AMR-associated.
- The total number and percentage of patients with AMR-associated deaths who die in hospital versus in the community.
- The percentage of AMR-associated deaths per medical specialty for patients who died in hospital. This will be calculated by dividing the total number of patients with AMR-associated deaths that were admitted under each medical specialty during their final admission with the total number of patients who were admitted under the same specialty during their final admission.
- The association between AMR and healthcare utilisation (mode of admission, duration of stay in hospital, ICU admission rates and duration of stay, life-support duration) will be explored by comparing inpatients who recorded AMR-associated deaths with inpatients who died of infection using multivariable analysis (linear and logistic regression).
- The total number and percentage of patients with AMR pathogens of interest in sterile sites within 28 days of death without infection being recorded in the pathway that led to death in the MCCD. ICD-10 diagnoses of infection during the final admission for this patient group will be described. The percentage of patients who recorded ICD-10 diagnoses infections during their final admission will be calculated.
- The total number of patients who had AMR documented in their death certificate (by using the ICD-10 codes U82-84).

Subgroup analyses will be performed for the following variables: age-group, sex, ethnicity, index of multiple deprivation decile.

Total number of infections will be adjusted according to the published EUSPAUR ascertainment factor for *E. coli* bloodstream infections (1.153 in 2022) to account for the difference between the total number of infections and the total number of infections captured by the AMR module with an available antibiogram (except for *Staphylococcus aureus* which has a separate individual ascertainment factor, 1.247 in 2022, and *Mycobacterium tuberculosis*, where reporting is mandatory). Ascertainment factors for *Klebsiella spp* and *Pseudomonas aeruginosa* are also show to be similar. For regional subgroup analysis, region-specific *E. coli* ascertainment factors will be used.[8] Number of deaths will also be adjusted for missing cases of patients under the National Data Opt Out (Ascertainment factor 1.057).

5.9 Patient and general public involvement:

We will attempt to engage with (British Society for Antimicrobial Chemotherapy, Antibiotic Research UK) to assess the acceptability of this research project among patients affected by AMR and inform study design. At the end of study, we will disseminate study findings back to these charities to share with patients.

We will conduct 10-20 face to face interviews with patients or relatives/carers of patients admitted to NHS hospitals and had recently had a drug resistant infection to assess the acceptability of the study, in particular with regards to accessing patient identifiable information.

5.10 Funding

This study will be funded by the UK Health Security Agency.

6. Data Handling and Management

The study is compliant with the requirements of General Data Protection Regulation (2016/679) and the Data Protection Act (2018). All investigators and study site staff will comply with the requirements of the General Data Protection Regulation (2016/679) with regards to the collection, storage, processing and disclosure of personal information, and will uphold the Act's core principles.

The project has been registered with the UCL Data Protection Office, reference number**:** **Z6364106 2024 02 73 health research**.

7. Peer and regulatory review

The study has been peer reviewed in accordance with the requirements outlined by UCL.

The Sponsor considers the procedure for obtaining funding from UKHSA to be of sufficient rigour and independence to be considered an adequate peer review.

Additionally, this study has been peer reviewed within and outside of UCL during the following occasions:

24/11/2023 Review of the study protocol by Nick Day, Policy and Programme Lead, National Medical Examiner System, NHS England.
19/12/2023 Online meeting with Laura Whitney and Chrstine Pinkard from NHS England in order to review study protocol.
20/1/2024 Review of protocol by Alexander Aiken from the London School for Hygiene and Tropical Medicine.
23/1/2024 Protocol discussed during the BSAC Council.
30/01/2024 Online meeting with Eirini Koutoumanou, medical statistician to discuss data analysis aspects of the study protocol.
02/02/2024 UCL ACF/ACF Academic meeting, protocol presented and discussed.
06/02/2024 UKHSA meeting with Colin Brown, Russell Hope, Rebecca Lester to discuss study protocol.

The study was deemed not to require regulatory approval from any regulatory bodies.

8. Monitoring and auditing

The Chief Investigator will ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol and ensure adequate data quality.

The Chief Investigator will inform the sponsor should he/she have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

9. Indemnity arrangements

University College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

10. Archiving

UCL and each participating site recognise that there is an obligation to archive study-related documents at the end of the study (as such end is defined within this protocol). The Chief Investigator confirms that he will archive the study master file at the UCL Data Safe Haven for the period stipulated in the protocol and in line with all relevant legal and statutory requirements.

11. Timeline

Study phases		2023	2024	2024	2024	2024	2025
		Q4	Q1	Q2	Q3	Q4	Q1
Developmental							
Protocol writing		x					
Local audit in UCLH to assess flowchart		x					
Funding acquisition		x					
Formative							
Obtain ethical approval from IRAS and local R&D approvals			x	x			
Data collection					x	x	
Analysis							
Data analysis						x	x

Dissemination							
Public Engagement			x				x
Manuscript preparation							x
Submission for publication							x
Submission for presentation in ECCMID							x
Monitoring and Evaluation							
Progress Monitoring, Meetings of study chief investigators and study collaborators.			x	x	x	x	x
Yearly Updates to Ethics Committee							x
Yearly updates to the Confidentiality Advisory Group							x
Yearly updates to study funder							x

12. Study budget

This is a budget for the entire length of the study and excludes any VAT if applicable.

	Total cost
NHSE data access charges	**£6,000**
UKHSA data access charges*	**£0**
Louis Grandjean (based on 5% time on project for 12 months)	**£5,647.8**
Ioannis Baltas (based on 10% time on project for 12 months)**	**£0**
Public and Patient involvement & Research dissemination activities	**£2,000**
Institutional Overhead Percentage (UCL 28%)	**£3,821.2**
Overall total	**£17,468**

*SGSS Data access, processing, and dissemination charges to be covered by UKHSA.

**Supported by NIHR Academic Clinical Fellowship

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14. Appendices

Supplementary table 1

Infectious syndrome	ICD-10 code	ICD-10 code description
Sepsis including bloodstream infections	A40	Streptococcal sepsis
	A41	Other sepsis
	A48.3	Toxic shock syndrome
	B37.7	Candidal sepsis
	O85	Puerperal sepsis
	P36	Bacterial sepsis of newborn
	R57.2	Septic shock
	R65.0	Systemic Inflammatory Response Syndrome of infectious origin without organ failure

	R65.1	Systemic Inflammatory Response Syndrome of non-infectious origin without organ failure
	A49.0	Staphylococcal infection, unspecified site
	A49.1	Streptococcal and enterococcal infection, unspecified site
	B37.8	Candidiasis of other sites
	B37.9	Candidiasis, unspecified
Peritoneal and intra-abdominal infections	A05.0	Foodborne staphylococcal intoxication
	K35	Acute appendicitis
	K36	Other appendicitis
	K37	Unspecified appendicitis
	K54.4	Diverticular disease of both small and large intestine with perforation and abscess
	K57.0	Diverticular disease of small intestine with perforation and abscess
	K57.2	Diverticular disease of large intestine with perforation and abscess
	K57.8	Diverticular disease of intestine, part unspecified, with perforation and abscess
	K61	Abscess of anal and rectal regions
	K65	Peritonitis
	K75	Abscess of liver
	K80.0	Calculus of gallbladder with acute cholecystitis
	K80.1	Calculus of gallbladder with other cholecystitis
	K80.3	Calculus of bile duct with cholangitis
	K80.4	Calculus of bile duct with cholecystitis
	K81	Cholecystitis
	K82.2	Perforation of gallbladder
	K83	Cholangitis
	K83.2	Perforation of bile duct
	N70	Salpingitis and oophoritis
	N73	Other female pelvic inflammatory diseases
	N98.0	Infection associated with artificial insemination
	O03.0	Spontaneous abortion : incomplete, complicated by genital tract and pelvic infection
	O04.0	Medical abortion : incomplete, complicated by genital tract and pelvic infection
	O05.0	Other abortion : incomplete, complicated by genital tract and pelvic infection
	O06.0	Unspecified abortion : incomplete, complicated by genital tract and pelvic infection
	O07.0	Failed medical abortion, complicated by genital tract and pelvic infection
	O08.0	Genital tract and pelvic infection following abortion and ectopic and molar pregnancy
	O41.1	Infection of amniotic sac and membranes
	O86.1	Other infection of genital tract following delivery
	P39.2	Intra-amniotic infection of fetus, not elsewhere classified
	P77	Necrotizing enterocolitis of fetus and newborn
	P78.0	Perinatal intestinal perforation
	P78.1	Other neonatal peritonitis
Diarrhoea	A02.0	Salmonella enteritis
	A03	Shigellosis
	A04.0	Enteropathogenic Escherichia coli infection
	A04.1	Enterotoxigenic Escherichia coli infection
	A04.2	Enteroinvasive Escherichia coli infection
	A04.3	Enterohaemorrhagic Escherichia coli infection
	A04.4	Other intestinal Escherichia coli infections
Tuberculosis	A15 – A19	Tuberculosis
	B20.0	HIV disease resulting in mycobacterial infection
	B90	Sequelae of tuberculosis
	K23.0	Tuberculous oesophagitis
	K67.3	Tuberculous peritonitis
	K93.0	Tuberculous disorders of intestines, peritoneum and mesenteric glands
	M01.1	Tuberculous arthritis
	M49.0	Tuberculosis of the spine
	M90.0	Tuberculosis of bone
	N33.0	Tuberculous cystitis
	N74.0	Tuberculous infection of cervix uteri
	N74.1	Female tuberculous pelvic inflammatory disease
	P37.0	Congenital tuberculosis
	P37.0	Congenital tuberculosis
Meningitis and other central nervous system infections	B37.5	Candidal meningitis
	G00	Bacterial meningitis, not elsewhere classified

	G03	Meningitis due to other and unspecified causes
	G04	Encephalitis, myelitis and encephalomyelitis
	G06	Intracranial and intraspinal abscess and granuloma
	G08	Intracranial and intraspinal phlebitis and thrombophlebitis
	H44.0	Purulent endophthalmitis
Infections of the skin and subcutaneous systems	A46	Erysipelas
	A48.0	Gas gangrene
	B37.2	Candidiasis of skin and nail
	B37.3	Candidiasis of vulva and vagina
	H05.0	Acute inflammation of orbit
	L00	Staphylococcal scalded skin syndrome
	L01	Impetigo
	L02	Cutaneous abscess, furuncle and carbuncle
	L03	Cellulitis
	L04	Acute lymphadenitis of face, head and neck
	L05.0	Pilonidal cyst with abscess
	L08	Other local infections of skin and subcutaneous tissue
	L89	Decubitus ulcer and pressure area
	L97	Ulcer of lower limb, not elsewhere classified
	M72.6	Necrotizing fasciitis
	N76.4	Abscess of vulva
	O86.0	Infection of obstetric surgical wound
	O91.0	Infection of nipple associated with childbirth
	O91.1	Abscess of breast associated with childbirth
	O91.2	Nonpurulent mastitis associated with childbirth
	P38	Omphalitis of newborn with or without mild haemorrhage
	P39.0	Neonatal infective mastitis
	P39.1	Neonatal conjunctivitis and dacryocystitis
	P39.4	Neonatal skin infection
Upper respiratory tract infections and related infections of the ear, nose and throat	H60.0	Abscess of external ear
	H60.1,	Cellulitis of external ear
	H60.2	Malignant otitis externa
	H60.3	Other infective otitis externa
	H60.8	Other otitis externa
	H60.9	Otitis externa, unspecified
	H65.0	Acute serous otitis media
	H65.1	Other acute nonsuppurative otitis media
	H65.2	Chronic serous otitis media
	H65.3	Chronic mucoid otitis media
	H65.9	Other chronic nonsuppurative otitis media
	H66.0	Acute suppurative otitis media
	H66.1	Chronic tubotympanic suppurative otitis media
	H66.2	Chronic atticoantral suppurative otitis media
	H66.3	Other chronic suppurative otitis media
	H66.4	Suppurative otitis media, unspecified
	H66.9	Otitis media, unspecified
	H68.0	Eustachian salpingitis
	H70.0	Acute mastoiditis
	H70.1	Chronic mastoiditis
	H70.2	Petrositis
	H70.8	Other mastoiditis and related conditions
	H70.9	Mastoiditis, unspecified
	H73.0	Acute myringitis
	H73.1	Chronic myringitis
	H83.0	Labyrinthitis
	J01	Acute Sinusitis
	J02	Acute pharyngitis
	J03	Acute tonsilitis
	J04	Acute laryngitis and tracheitis
	J05	Acute obstructive laryngitis [croup] and epiglottitis
	J06	Acute upper respiratory infections of multiple and unspecified sites
	J36	Peritonsillar abscess

	K04.6	Periapical abscess with sinus
	K04.7	Periapical abscess without sinus
	K11.3	Abscess of salivary gland
	K12.2	Cellulitis and abscess of mouth
Endocarditis and other cardiac infections	B37.6	Candidal endocarditis
	H30.1	Infective pericarditis
	I33	Acute and subacute endocarditis
	I38	Endocarditis, valve unspecified
	I40	Acute myocarditis
Lower respiratory infections and all related infections in the thorax	B37.1	Pulmonary candidiasis
	J09-J18	Influenza and pneumonia
	J20-J22	Other acute lower respiratory infections
	J41	Simple and mucopurulent chronic bronchitis
	J44.0	Chronic obstructive pulmonary disease with acute lower respiratory infection
	J44.1	Chronic obstructive pulmonary disease with acute exacerbation, unspecified
	J69.0	Pneumonitis due to food and vomit
	J85	Abscess of lung and mediastinum
	J86	Pyothorax
	P23.2	Congenital pneumonia due to staphylococcus
	P23.4	Congenital pneumonia due to Escherichia coli
	P23.5	Congenital pneumonia due to Pseudomonas
	P23.6	Congenital pneumonia due to other bacterial agents
	P23.8	Congenital pneumonia due to other organisms
	P23.9	Congenital pneumonia, unspecified
	U07.1	COVID-19, virus identified
	U07.2	COVID-19, virus not identified
Infections of bone, joints, and related organs	M00	Pyogenic arthritis
	M46.3	Infection of intravertebral disc (pyogenic)
	M60.0	Infective myositis
	M65.0	Abscess of tendon sheath
	M65.1	Other infective (teno)synovitis
	M71.0	Abscess of bursa
	M71.1	Other infective bursitis
	M86	Osteomyelitis
	T84.5	Infection and inflammation due to internal joint prosthesis
Urinary tract infections and pyelonephritis	B37.4	Candidiasis of other urogenital sites
	N10	Acute tubulo-interstitial nephritis
	N11	Chronic tubule-interstitial nephritis
	N12	Tubulo-interstitial nephritis, not specified as acute or chronic
	N13.6	Pyonephrosis
	N15.1	Renal and perinephric abscess
	N30.0	Acute cystitis
	N30.8	Other cystitis
	N34.0	Urethral abscess
	N39.0	Urinary tract infection, site not specified
	N39.0	Urinary tract infection, site not specified - Urosepsis
	N41.0	Acute prostatitis
	N41.1	Chronic prostatitis
	N41.2	Abscess of prostate
	N45	Orchitis and epididymitis
	N49	Inflammatory disorders of seminal vesicle
	O23	Infections of genitourinary tract in pregnancy
	O86.2	Urinary tract infection following delivery
	O86.3	Other genitourinary tract infections following delivery
	P39.3	Neonatal urinary tract infection
Typhoid, paratyphoid, and invasive non-typhoidal Salmonella	A01	Typhoid and paratyphoid fevers
	A02.1	Salmonella sepsis
	A02.2	Localized salmonella infections

	A02.8	Other specified salmonella infections
	A02.9	Salmonella infection, unspecified
Resistance codes	U82	Resistance to betalactam antibiotics
	U83	Resistance to other antibiotics
	U84	Resistance to other antimicrobial drugs

Supplementary table 2

Supplementary Table 1: Compatible combinations of pathogen of interest and infectious syndrome.									
Infectious syndrome		MRSA	VRE	PTSP	Ent[1]	CRAB	MDR-PA	Mtb	Can
Sepsis including bloodstream infections		x	x	x	x	x	x	x	x
Peritoneal and intra-abdominal infections		x	x	x	x	x	x	x	x
Diarrhoea		-	-	-	x	-	-	-	-
Tuberculosis		-	-	-	-	-	-	x	-
Meningitis and other central nervous system infections		x	-	x	x	x	x	x	x
Infections of the skin and subcutaneous systems		x	x	x	x	x	x	x	-
Upper respiratory tract infections and related infections of the ear, nose and throat		x	-	x	x	x	x	x	-
Endocarditis and other cardiac infections		x	x	-	x	-	x	-	x
Lower respiratory infections and all related infections in the thorax		x	x	x	x	x	x	x	-
Infections of bone, joints, and related organs		x	x	x	x	x	x	x	x
Urinary tract infections and pyelonephritis		x	x	x	x	x	x	x	x
Typhoid, paratyphoid, and invasive non-typhoidal Salmonella		-	-	-	x	-	-	-	-

X denotes compatibility. MRSA: Methicillin-resistant *Staphylococcus aureus*; VRE: Vancomycin-resistant enterococci; PTSP: Penicillin-tolerant *Streptococcus pneumoniae*; Ent: Enterobacterales; Carbapenem-resistant *Acinetobacter baumanii*; MDR-PA: MDR *Pseudomonas aeruginosa*; Mtb: *Mycobacterium tuberculosis*; Can: *Candida spp. For non-diarrhoea diseases Shigella spp and non typhoidal Salmonella spp are excluded. For diarrhoeal diseases Escherichia coli,Salmonellosis from nontyphoidal Salmonella, Shigella spp are included only. For Typhoid, paratyphoid, and invasive non-typhoidal Salmonella only Typhoidal or invasive non-typhoid Salmonella spp from Enterobacterales are included.* Table is based on previous classification.[26] The pathogen-infection syndrome combinations were aligned with the ones described by Mohsen et al.[26]

Supplementary table 3

Infectious syndrome	Diagnostic specimen sites
Sepsis including bloodstream infections	Blood, CSF, tissue, sterile fluid
Peritoneal and intra-abdominal infections or diarrhoea	Blood, tissue, sterile fluid (ascitic, biliary, gallbladder, peritoneal, drain, abdominal), stool culture
Tuberculosis	All samples with pathogen of interest
Diarrhoea	Blood, stool culture
Meningitis and other central nervous system infections	Blood, CSF, tissue
Infections of the skin and subcutaneous systems	Blood, wound swab, tissue, sterile fluid (abscess)
Upper respiratory tract infections and related infections of the ear, nose and throat	Blood, ear swab, throat swab, tissue, sterile fluid, implant
Endocarditis and other cardiac infections	Blood, tissue, sterile fluid (pericardial), implant
Lower respiratory infections and all related infections in the thorax	Blood, sputum, bronchoalveolar lavage, tissue, sterile fluid (pleural)
Infections of bone, joints, and related organs	Blood, tissue, sterile fluid (joint), implant
Urinary tract infections and pyelonephritis	Blood, urine, tissue
Typhoid, paratyphoid, and invasive non-typhoidal Salmonella	All samples with pathogen of interest

Supplementary table 4

Infectious syndrome informative ranking hierarchy (Organised from most informative (top) to least (bottom) – Adapted from *Naghavi et al*[1,26]
Meningitis and other bacterial central nervous system infections
Endocarditis and other cardiac infections
Peritoneal and intra-abdominal infections or diarrhoea
Lower respiratory infections and all related infections in the thorax
Upper respiratory tract infections and related infections of the ear, nose and throat
Infections of bone, joints, and related organs
Typhoid, paratyphoid, and invasive non-typhoidal Salmonella
Diarrhoea
Urinary tract infections and pyelonephritis
Bacterial infections of the skin and subcutaneous systems
Tuberculosis
Sepsis including bloodstream infections