Carbapenem Resistant Enterobacterales Descriptive Infection Trainee Study

Project Acronym: CRE-DITS

Version Control

Version:	Version 1.4
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Supported by:

The National Infection Team Collaborative for Audit and Research (NITCAR)

PROTOCOL VERSIONS

Version Stage	Versions No	Version Date	Protocol updated & finalised by;	Appendix No detail the reason(s) for the protocol update
Current	V.14	9/11/2024	Dr Ioannis Baltas Dr Thomas Harrison Dr Katie Drury Dr Andrew Kirby Professor Louis Grandjean Dr Jonathan Cattrall Dr Nathan Moore	Updated publication policy
Previous	V1.3	5/11/2024	Dr Ioannis Baltas Dr Thomas Harrison Dr Katie Drury Dr Andrew Kirby Professor Louis Grandjean Dr Jonathan Cattrall Dr Nathan Moore	Clinical metadata categories defined further Clarification on minimum samples required from each centre to participate
Previous	V1.2	27/10/2024	Dr Ioannis Baltas Dr Thomas Harrison Dr Katie Drury Dr Andrew Kirby Professor Louis Grandjean	Updated aims Updated authorship policy Updated data handling and management
Previous	V1.1	08/10/2024	Dr Ioannis Baltas Dr Thomas Harrison	Study catchment increased to UK

				Updated Objectives Aztreonam-avibactam added to list of new drugs
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Previous	V1	02/10/2024	Dr Ioannis Baltas	N/A

PROJECT SUMMARY

Identifiers	
IRAS Number	N/A
REC Reference No	N/A
Sponsor Reference No	TBC
Other reference number(s) (if applicable)	N/A
Full (Scientific) title	Carbapenem Resistant Enterobacterales Descriptive Infection Trainee Study
Health condition(s) or problem(s) studied	Infection, Antimicrobial resistance
Project Type i.e. Cohort etc	National Prospective multicentre audit
Target sample size	5250 isolates (Target 35 sites with 150 isolates each on average)
PROJECT TIMELINES	
Project Duration/length	12 months
Expected Start Date	01/11/2024
End of project definition and anticipated date	01/11/2025
Key project milestones	NITCAR approval: October 2024 Start of site enrolment: November 2024 Data collection completion: May 2025
FUNDING & Other	
Funding	This study will receive no dedicated funding and will performed as part of our routine work
Other support	None
KEY PROJECT CONTACTS	
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KEY WORDS

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.

Enterobacterales: An order of Gram-negative, non-spore forming, facultatively anaerobic, rod-shaped bacteria with the class Gammaproteobacteria. Members of the order known to cause common infections in humans include Escherichia coli, Klebsiella spp, Enterobacter spp and Citrobacter spp.

Minimum inhibitor concentration: the lowest concentration of a chemical, usually a drug, which prevents visible *in vitro* growth of bacteria. MIC50 and MIC 90 are defined as the minimum concentration at which 50% and 90% of the isolates are inhibited.

LIST OF ABBREVIATIONS

AMR	Antimicrobial Resistance
BMD	Broth microdilution
CI	Chief Investigator
CRE	Carbapenemase-resistant Enterobacterales
DD	Disc diffusion
EUCAST	European Committee on Antimicrobial Susceptibility Testing
IDSA	Infectious Diseases Society of America
IMP	Imipenemase
MBL	Metallo-β-lactamase
MIC	Minimum Inhibitory Concentration
NDM	New Delhi metallo-beta-lactamase
PI	Principle Investigator
REC	Research Ethics committee
VIM	Verona integron-encoded metallo-β-lactamase
WHO	World Health Organisation

CONTENTS

Background and rationale

AMR refers to when bacteria, viruses, fungi and parasites no longer respond to antibiotic medicines. AMR has been described as the silent pandemic and has been listed as a top 10 threat to humanity by the WHO.[1] It is estimated to have caused 1.27 million deaths in 2019 and is projected to cause 10 million deaths every year by 2050.[2,3] Infections from antibiotic resistant organisms are associated with higher risk of death, disability and longer stay in hospital compared to infections from antibiotic sensitive organisms, as well as significantly higher healthcare costs.[4]

Among antibiotic resistant bacteria, carbapenem resistant Enterobacterales (CRE) constitute a particularly challenging threat. Currently, they are listed as critical priority pathogens by the WHO, as they exhibit multi-drug resistant profiles including resistance to carbapenems, which are considered last line antimicrobials for the treatment of Gram-negative infections.[5] CRE become resistant to carbapenems via a variety of mechanisms, including alteration of outer membrane permeability, drug efflux, target site mutations and production of carbapenemases.[6] Among these resistance mechanisms, the last one is considered the most important, as it can confer high levels of carbapenem resistance, rendering the drugs completely ineffective. Additionally, carbapenemase-encoding genes are typically harboured onto plasmids, which can spread among different bacteria, leading to further infections.[7] For this reason, knowing whether a CRE produces a carbapenemase is important for selecting the appropriate treatment, as well as to limiting the spread of AMR.

Treatments for CRE infections have traditionally included combinations of older, non-beta lactam based drugs, which typically have increased toxicity and limited efficacy, leading to poor patient outcomes.[8] Over the last 10 years, new beta-lactam-based antimicrobials have been introduced for the treatment of CRE infections, leading to improved patient outcomes. These include meropenem-vaborbactam and imipenem relebactam, which are active against KPC-producing CRE, ceftazidime-avibactam, which is active against KPC- and OXA-48 producing CRE and cefiderocol, which has activity against all types of CRE, including MBL producers.[9,10] The combination of ceftazidime-avibactam with aztreonam has also been recommended for the treatment of MBL-producers, while aztreonam-avibactam is due to be launched in 2024.[11] Yet, resistance to new agents has already been described.[10,12] Knowing the resistance epidemiology of CRE to new and older agents in the United Kingdom is important to guide empirical treatment, while final AST is pending. Despite this, resistance profiles of CRE are not published as part of the annual ESPAUR report for AMR in England.

Aims and objectives

Aims

➢ Describe the laboratory testing practises and resistance profiles of CRE to new and older antimicrobials among multiple centres in the United Kingdom.

Objectives

➢ Describe the percentage of CRE in the United Kingdom that have been tested for the presence of a carbapenemase.

➢ Describe the percentage of CRE in the United Kingdom that produce a carbapenemase

➢ Describe the percentage of CRE that have been tested for susceptibility to new antimicrobials (cefiderocol, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, aztreonam-avibactam).

➢ Describe the antimicrobial resistance profile of CRE to older and newer antimicrobials in order to identify treatment options for patients with CRE infections.

Project design

National prospective multicenter audit designed and conducted to produce information to inform delivery of best care for patients with carbapenem-resistant infections.

Audit standards

1. CRE has been tested for the production of carbapenemases (Target 100%). Audit standard reference: UK Standards of Microbiological Investigations No60: Detection of bacteria with carbapenem-hydrolysing β-lactamases (carbapenemases)[13]

2. KPC-producing CRE have been tested for susceptibility to ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, cefiderocol (Target 100%). Audit standard reference: IDSA 2024 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections[14]

3. OXA-48 producing CRE have been tested for susceptibility to ceftazidime-avibactam and cefiderocol (Target 100%). Audit standard reference: IDSA 2024 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections[14]

4. MBL-producing CRE have been tested for susceptibility to cefiderocol, and for ceftazidime-avibactam and aztreonam synergy. Audit standard reference: IDSA 2024 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections[14]

Project locations and authorship policy

All infectious diseases and/or clinical microbiology departments in the UK are encouraged to participate in this project. Participation of infection trainees will be prioritised but in departments where numbers of trainee are limited other infection specialists (Consultants in Infections, AMS Pharmacists etc.) will be eligible to participate. Authorship policy will follow the NITCAR principles (https://nitcollaborative.org.uk/wp/documents/). The project management group, and others who

may become involved in data analysis and manuscript writing, and meet the ICJME criteria for authorship will be cited as authors for all publications. From each participating site, provided a complete dataset of CRE during the study period and within study timelines is submitted, including numbers of excluded isolates, two local investigators will be cited as PubMed citeable collaborative authors under the "CREDITS collaborative" heading. Additional collaborative authors may be added if the hospital makes a larger contribution (>200 isolates). Those involved in the project in a purely supervisory capacity e.g. supervision of trainees without data collection/analysis, will be listed in the acknowledgements section of a manuscript only. This planned publication policy describes the intended publication policy. This policy may be subject to modification e,g. based on specific journal requirements by the named study investigators.

Population

Consecutive non-duplicate CRE reported during routine clinical practice by collaborating Trusts' clinical microbiology laboratories between 01/10/2023 and 30/9/2024 will be eligible for inclusion. Duplicate samples, referring to CRE of the same species from the same patient within the project period, will be excluded. No other exclusion criteria will apply. CRE from any sample type will be eligible for inclusion.

Sample size

The NITCAR network will aim to recruit as many NHS Trusts as possible for participation in the project. Preliminary data from a large London teaching hospital suggest 150-200 non-duplicate CRE isolates would have been eligible for the project in 2022. Therefore each project site is expect to contribute 50-250 CRE isolates. This is an estimation and every NHS Trust in England is eligible to participate as long as all eligible CRE isolates in the study period as submitted, irrespective of total numbers.a

Antimicrobial susceptibility testing (AST)

Results of AST will be recorded as performed locally and may include testing by DD, gradient diffusion or BMD. EUCAST breakpoints as the time of reporting will be used for interpretation. For ceftazidime-avibactam and aztreonam combination the presence or absence of vitro synergy will be reported. AST testing methods for the newer agents will be recorded if available.

Clinical metadata

Minimal clinical metadata will be collected in order to ensure samples remain fully anonymised and will include:

- Sample type (Blood, faeces, sterile fluid, sterile tissue, sputum, bronchoalveolar lavage, urine, skin swab, wound swab, line tip, other)
- Sample date
- Sample specialty (medicine, surgery, haematology, oncology, infectious diseases, intensive care, paediatrics, emergency medicine, primary care, other)
- Sample collection location (inpatient, outpatient)
- Project site location. Data will be aggregated to regional level for regions with more than 5 participating Trusts to avoid identification and to national level for regions with less than 5 participating Trusts.

If the same isolate is identified simultaneously (within 14 days) from multiple sites in a single patient, samples for enrolment will be selected according to the following hierarchical order of sample types (from highest to lowest):

1. Blood
2. Sterile fluids or tissues
3. Central venous catheter tips
4. Bronchoalveolar lavage
5. Sputum/Upper respiratory samples
6. Urine
7. All other non-sterile sites
8. Screening samples (rectal screens, etc)

Statistical analysis plan

Levels of resistance to each agent will be reported using percentages. MIC50 and MIC90 results will be reported. Subgroup analysis according to sample type and sample collection location will be performed.

Ethics and consent

The Health Research Authority checklist was used to confirm that this project is not considered research and no REC approval is required. The project will use fully anonymised clinical isolates and does not aim to generate generalisable findings. Therefore explicit patient consent will not be sought. Relevant local approvals in each site will be sought.

Eligibility criteria

Inclusion Criteria

➢ CRE (Enterobacterales resistant to at least one of the following drugs: meropenem, imipenem, ertapenem) isolated in a clinical culture of a project site within the project period (01/10/2023 – 30/9/2024).

Criteria

➢ CRE of the same species from the same patient will be excluded. Project sites will keep a local record of numbers of excluded duplicate samples.

Funding and supply of equipment

This project will receive no external funding and will require no additional equipment.

Data handling and management

Data in each collaborating centre will be collected in a dedicated Microsoft Excel data collection form. Centres will follow local governance approval pathways before submitting data. No patient identifiable information will be recorded on the data collection tool. Individual site project logs will be stored locally as per current local information governance arrangements. Central project logs will be stored in password-protected NHS computers. They will contain no patient-identifiable information. There we

be no hard-copy records from this project. Data will transferred using NHS emails with standard encryption. All Excel forms with be password protected. Data management and data security will abide by the requirements of the General Data Protection Regulations (GDPR) and any subsequent amendments.

Confidentiality

No patient identifiable data will be recorded. All data collected about patient isolates will be identified using only a unique project number. This number will be allocated on the data collection tool by the local team once a record is created. Any correspondence between the project management group and the participating centres will only use this unique project number. The linkage between the database project ID and the actual patients will be confidentially maintained at the participating site as per local arrangements. This data will not be submitted to the project office and will not be sent outside of the participating site. The patients identified for this project will not be identifiable in any future publication that results from this project.

Material/sample storage

There will be no material or samples generated or processed as part of this project.

Patient and public involvement

Patients and the public were not engaged in setting up this project, however, treatment of drug resistant infections has been prioritised by multiple different patient groups.

Peer and regulatory review

This project is under the umbrella of The National Infection Teams Collaborative for Audit and Research (NITCAR), consultant chair Dr Andrew Kirby. The aggregated data will be available for the audit group to review. The project has been presented and peer reviewed during the monthly NITCAR meetings on the 17/09/2024 and 17/10/2024.

Dissemination of findings

The results of this study will be submitted to a peer reviewed scientific journal. The results will also be presented at national and international conferences.

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12   Qiao, S. *et al.* A large-scale surveillance revealed that KPC variants mediated ceftazidime-avibactam resistance in clinically isolated Klebsiella pneumoniae. *Microbiology Spectrum* **12**, e00258-00224 (2024).

13   Public Health England. UK Standards for Microbiology Investigations Detection of bacteria with carbapenem-hydrolysing β-lactamases (carbapenemases) (2022).

14   Aitken, S. L. & Clancy, C. J. IDSA Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections. (2020).