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Surveillance of carbapenem resistance in Asian countries: a systematic review and meta-analysis

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ABSTRACT

Introduction Carbapenems are used to treat multidrug-resistant organisms as last-resort antibiotics. Resistance to carbapenems is an emerging public health threat worldwide, with alarming reported rates in Asian countries. To minimise further spread of resistant strains and guide interventions, it is important to understand the prevalence rates and causative molecular determinants. Therefore, the systematic review and meta-analysis arising from this protocol will aim to comprehensively describe the available surveillance data on carbapenem resistance in Asian countries to provide an in-depth overview of the carbapenem resistance status in this region.

Methodology and analysis A systematic review and meta-analysis will be conducted via PubMed, ScienceDirect, Cochrane Library and Web of Science databases. Additional articles and grey literature will be searched in Google Scholar, OpenGrey and Google Chrome by manually searching the reference lists of selected studies. The review question was designed according to components in the ECLIPSE (E-expectations, C-client, L-location, I-impact, P-profile and S-service) framework. Studies conducted with samples other than clinical samples will be excluded. Only original articles published in the English language will be included. The Joanna Briggs Institute critical appraisal tool will be used to assess the quality of the included studies. A random-effects meta-analysis will be performed if the data are sufficiently homogenous. Heterogeneity between studies will be assessed via the I^2 statistic. The subgroup analysis will be performed considering the type of sample, pathogen type, region/country where the studies were conducted and genetic determinants.

Ethics and dissemination As this study is conducted on the basis of published data, ethical approval is exempt. The findings of this study will be disseminated in a peer-reviewed journal with the intention of providing summarised data on the globally emerging threat of carbapenem resistance and emphasising the need to introduce alternative, more effective treatment options.

PROSPERO registration number CRD42024515806.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will potentially inform the carbapenem resistance rates reported from studies published in the past 10 years and the trends of increasing resistance rates with the causative genetic determinants.
⇒ The search strategy was developed with the help of subject experts considering Medical Subject Heading terms related to the current review title by referring to the published literature, and data from hospital antibiograms and antimicrobial resistance surveillance database repositories will not be included since we have no access to these databases.
⇒ Article screening, data extraction and quality assessment of selected studies will be conducted by two independent reviewers with experience in systematic review and meta-analysis methodology.
⇒ If the data are sufficient and homogenous, random effects meta-analysis will be performed with the I^2 statistic, to assess the heterogeneity between studies.
⇒ Since studies published in the English language over the past ten years will be reviewed extensively, language bias and publication year bias will be introduced as limitations.

INTRODUCTION

Antimicrobial resistance (AMR) is a global concern that poses a significant threat to the public health and healthcare systems worldwide.[1] An alarming rate of AMR has been reported in the Global Antimicrobial Resistance and Use Surveillance System report published in 2022.[2] The development of AMR causes antibiotics to be less effective or ineffective, which renders treatment challenging or impossible. As a result, the risk of further spread of infections increases, leading to severe illnesses, disability and ultimately death.[3] It is estimated that bacterial AMR was directly associated with 1.27 million global deaths in 2019.[3]

Carbapenems are considered the last-resort antibiotics for the treatment of multidrug-resistant (MDR) organisms, which exhibit a broad spectrum of activity against many Gram-positive bacteria, Gram-negative bacteria (GNB) and anaerobes.[4] The mechanism of action of carbapenems is similar to that of other beta-lactam antibiotics, which function by binding and deactivating

penicillin-binding proteins (PBPs) and preventing bacterial cell wall synthesis.[5] The commonly available carbapenem antibiotics are imipenem, meropenem, doripenem and ertapenem. Owing to the increasing rates of antibiotic resistance, the utilisation of carbapenems has also increased, leading to carbapenem resistance.[4 6]

Carbapenem resistance was first described in 1996 with the identification of carbapenemase-producing *Klebsiella pneumoniae*.[7–12] According to recent WHO records, the Organisation for Economic Cooperation and Development has predicted that resistance rates to these last-resort antibiotics will double from 2005 to 2035.[13] The mortality and morbidity associated with infections caused by carbapenem-resistant organisms (CROs) are higher than those associated with infections caused by the carbapenem-susceptible organisms.[8 14] Carbapenem resistance often arises via different mechanisms such as the production of carbapenemases by the acquisition of carbapenem resistance genes, efflux pumps and mutations that change the expression and/or function of porins and PBPs. Among these mechanisms, the acquisition of carbapenem resistance genes is the most common mechanism.[4 8 9 15] Carbapenamses are classified into different Ambler classes, A, B, C and D on the basis of their protein sequence. The globally significant carbapenemases include *Klebsiella pneumoniae* carbapenemases (KPC), Verona intergron-encoded metallo-beta-lactamase (VIM), imipenem metallo-beta-lactamase (IMP), New Delhi metallo-beta-lactamase (NDM) and oxacillinase-48 (OXA-48).[16]

Limited treatment options are currently available for CROs, including colistin and tigecycline. However, strains resistant to these two antibiotics have also been reported. As carbapenems are used to treat infections caused by MDR-GNB, the development of resistance is life-threatening. Thus, this study aims to describe the surveillance of CROs in Asian countries along with the prevalence and spread of carbapenem resistance genes. To the best of our knowledge, this is the first systematic review and meta-analysis on the surveillance of carbapenem resistance in Asian countries. Therefore, there is an urgent need for strong antimicrobial stewardship programmes to combat the threat of carbapenem resistance.

Objectives

This review aims to identify the surveillance rates of CRO among different clinical samples, different pathogens and different regions/countries and the reported genetic determinants in each country.

METHODS AND ANALYSIS

This protocol was registered in International Prospective Register of Systematic Reviews (PROSPERO) on 2 March 2024 (CRD42024515806). Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines will be followed for conducting and reporting of the study.

Eligibility criteria

The review question was decided according to the ECLIPSE (E-expectations, C-client, L-location, I-impact, P-profile and S-service) framework.[17] The inclusion criteria will be published studies conducted in Asian countries, studies conducted with only clinical isolates, studies published in English, and without considering the number of isolates tested in each study, the studies conducted between 1 January 2014 and 31 January 2024 . Studies that will be fulfilling the following criteria will be excluded: studies that reported data on the prevalence of carbapenem resistance (CR) in Asian countries; studies that reported rates of resistance to antibiotics other than carbapenems; publications other than original studies, including reviews, editorials, commentaries, notes and conference proceedings and animal studies. The reasons for exclusion will be recorded for each reference screened.

Expectations

To describe the surveillance of carbapenem resistance in Asian countries and related genetic determinants.

Client group

Patients were diagnosed with an infection caused by CRO, particularly carbapenem-resistant *Klebsiella* spp., carbapenem-resistant *Escherichia coli*, carbapenem-resistant *Acinetobacter* spp, carbapenem-resistant *Pseudomonas* spp and other carbapenem-resistant GNB.

Location

Asia.

Impact

To identify carbapenem resistance rates among different Asian countries and report their genetic characteristics.

Professionals involved

Healthcare professionals and patients.

Service

Updating the available knowledge on carbapenem resistance.

Study characteristics

This systematic review and meta-analysis will include observational (cohort, cross-sectional and case-control), retrospective and prospective studies reporting data on the surveillance of carbapenem resistance in Asian countries. Studies conducted with isolates other than clinical samples will be excluded.

Definitions

The term ‘carbapenem resistance prevalence’ is defined as the proportion of reported carbapenem-resistant cases in the time period between 1 January 2014 and 31 January

2024, regardless of when they first developed carbapenem resistance (Health, 2024).[18]

Time frame

We will include published studies over the past 10 years from 1 January 2014 to 31 January 2024. The study was started on 1 February 2024 and planned to be completed by 1 August 2024. However, there were changes in the study duration due to several practical issues. An update search in the same databases will be performed prior to the completion of the final analysis and if any relevant studies that match the inclusion and exclusion criteria are identified, they will be included in the study.

Reporting characteristics

Only original studies published in the English language will be included.

Information sources

The PubMed, ScienceDirect, Cochrane Library and Web of Science will be searched to identify the related literature, and the English language was added as a filter. Google Scholar, OpenGrey and Google Chrome will be used to search for grey literature. Moreover, additional publications related to the research question will be identified by manual search of reference lists of the selected studies.

Search strategies

The search strategy was developed by the reviewers, with the help of subject experts. Commonly used terms and phrases related to the current review title were identified by referring to published literature along with Medical Subject Heading terms, and data from hospital antibiograms and AMR surveillance database repositories will not be included since we have no access to these databases. Initially, the search strategy was developed for the PubMed search and then will be modified according to other databases. The search strategy for the PubMed search is available in online supplemental file 1).

Study records

Selection process

Duplicates will be removed via the Endnote reference management software. The identified studies from different databases will be uploaded to the Rayyan web-based application. Titles and abstracts will be screened by two independent reviewers. The first round of screening will be as comprehensive as possible to find appropriate research studies that match the eligibility criteria and to capture a wide range of literature. The reviewers will be blinded to each other's decisions during the review process. The conflicts will be discussed by two reviewers and will reach a consensus. In addition, the reference lists of selected studies will be manually searched to find further eligible studies. The full texts of the initially selected studies will be subsequently screened by the same two independent reviewers. The conflicts will be discussed and will reach a consensus or will be discussed by a third senior reviewer. The process of study selection will be detailed in a PRISMA flow chart.

Data items

Relevant information under the following categories will be extracted from each of the selected studies: name of the study, first author, study design, study period, study population, sample size, specimen type, names of the pathogens identified, type of carbapenem antibiotic used, prevalence rate and genes detected.

Data extraction

Data extraction will be performed independently by the two reviewers who have experience in systematic reviews, and the extracted data will be entered into the extraction form (online supplemental file 2). The conflicts between the resulting two extraction sheets will be discussed by a third senior reviewer.

Risk of bias assessment

The quality of the included studies will be assessed independently by two reviewers via the Joanna Briggs Institute (JBI) critical appraisal tool. However, some questions from the JBI tool, such as those related to carbapenem resistance assessment, may not be directly applicable to our study. Carbapenem resistance will be assessed only by considering qualitative interpretations, such as sensitive, intermediate or resistant. The zone diameters from disk diffusion, Minimum Inhibitory Concentration (MIC) s from dilution methods etc, will not be considered for interpretation. Studies with an overall score of ≤50% will be classified as low quality (ie, high risk of bias). Egger's test will be used to evaluate the presence of publication bias and will be presented with a funnel plot. A p value <0.05 will be considered as the cut-off for statistical significance. Two independent reviewers will be involved in the quality assessment. Disagreements between reviewers will be resolved by discussions between reviewers or after discussion with a third senior member of the review team. The level of credibility of the included studies will be interpreted in a table.

Data synthesis

Strategy for data synthesis and subgroup analysis

A random-effects meta-analysis will be performed if the data are sufficiently homogenous. If the resulting data are insufficient to conduct a meta-analysis, we will intend to perform a systematic review. If a meta-analysis is performed, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach will be used to grade the quality of the resulting evidence.

The subgroup analysis will be performed considering the type of sample, source of infection, hospital-acquired or community-acquired status, pathogen type, region/country where the studies were conducted and the reported genetic determinants. The heterogeneity of findings will be assessed by the I^2 statistic (I^2 >75% will be considered substantial heterogeneity). Meta-regression will be performed to investigate the effects of subgroups,

and sensitivity analysis will be performed. Statistical analysis will be performed via SPSS V.29 software.

Expected outcomes

Asia is the largest continent in the world with the highest population. Therefore, identifying the prevalence of carbapenem resistance in Asia is highly important. The findings of this study will help clinicians to implement infection control policies to prevent further spread of resistance genes and to identify alternative antibiotic options for updating the prevailing treatment guidelines. In addition, it will help to estimate the economic burden of managing antibiotic resistance. Antibiotic stewardship programmes can also be designed to understand the extent of antibiotic resistance and to guide appropriate antibiotic use.

Patient and public involvement

Neither patient nor public involvement is present in any of the study designs, conducting, reporting or dissemination plans of this systematic review and meta-analysis.

Ethics and dissemination

As this study is conducted on the basis of published data, ethical approval is exempt. The findings of this study will be disseminated in a peer-reviewed journal with the intention of providing summarised data on the globally emerging threat of carbapenem resistance.

DISCUSSION

The Asia-Pacific region is considered a hot spot for the emergence and spread of AMR, which is home to two-thirds of the world's population and ten of the least developed countries. Most people rely on over-the-counter medicines without prescriptions and tend to use broad-spectrum antibiotics even for simple infections, causing the emergence of AMR, including resistance to carbapenem antibiotics.[19] Carbapenem resistance is considered a significant public health threat, particularly in countries such as India, where the prevalence is relatively high.[20 21] Therefore, the aim of this systematic review and meta-analysis is to gather surveillance data on carbapenem resistance and to provide updated insights into current trends in carbapenem resistance.

This review arising from the protocol will comprehensively describe the extent of carbapenem resistance in Asian countries. Furthermore, it will help to identify gaps in current knowledge to minimise further dissemination of carbapenem resistance. The identification of countries with a lack of surveillance data may guide future research and support improving the prevailing understanding of the drivers of carbapenem resistance in those countries. Comparative analysis of reported data from different countries is also valuable, as it helps to identify resistance patterns in different countries, which makes it possible to vary in terms of antibiotic usage practices, healthcare facilities and economic strength. Therefore, targeted interventions and antibiotic prescription-related policies matching with specific needs of each country can be tailored. Synthesising data from multiple studies provides more accurate rates of prevalence with geographical and temporal trends. This information is crucial in resource allocation and in guiding healthcare interventions.

However, including studies published in the English language may result in not capturing some of the valuable studies published in non-English speaking countries, which is a limitation of this study. In conclusion, the systematic review and meta-analysis arising from this protocol are important for comprehensively describing the available data on the surveillance of carbapenem resistance, contributing to the implementation of effective strategies for combatting carbapenem resistance in Asian countries.

Contributors NJ and TNS conceptualised the study. NJ, SSD, DN and TNS participated in the study design. NJ drafted the original manuscript. All the authors contributed to the revision of the manuscript and approved the final version. The corresponding author (TNS) is the guarantor and attests that all the listed authors meet authorship criteria.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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Supplementary file 1

Search strategy for PubMed

1. 'Surveillance' OR 'Prevalence' OR 'Prevalence rate' OR incidence' OR 'occurrence'

2. "Carbapenem resist*" OR "Carbapenemase" OR "Carbapenem non susceptible"

3. Asia OR "Asian countries" OR "South Asia" OR "Sri Lanka", OR "India" OR "Bangladesh" OR "Pakistan", OR "Afghanistan" OR "Nepal", OR "Bhutan" OR "Maldives" OR "Iran", OR "China", OR "Japan", OR "Korea", OR "Mongolia" OR "Indonesia", OR "Philippines", OR "Vietnam", OR "Thailand", OR "Myanmar", OR "Malaysia", OR "Cambodia" OR "Laos" OR "Singapore", OR "Timor-Leste" OR "Brunei" OR "Turkey", OR "Iraq", OR "Saudi Arabia:" OR "Yemen" OR "Syria" OR "Jordan" OR "Azerbaijan" OR "United Arab Emirates" OR "Israel", OR "Qatar", OR "Oman", OR "Georgia", OR "Kuwait", OR "Armenia", OR "Bahrain", OR "Cyprus" OR "Palestine", OR "Uzbekistan", OR "Kazakhstan", OR "Turkmenistan", OR "Tajikistan" OR "Kyrgyzstan" OR "Russia".

4. 2014 to 2024

5. 1 AND 2 AND 3 AND 4

Supplementary file 2

Data extraction sheet

Name of the study	First author	Study design	Study period	Study population	Sample size	Specimen type	Source of infection	Pathogens isolated	Carbapenem antibiotic used	Antibiotic susceptibility testing method	Prevalence rate	Genes detected	Comments