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# EpideMiology and control measures of outBreaks due to Antibiotic-Resistant orGanisms in EurOpe (EMBARGO): a systematic review protocol

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## ABSTRACT

**Introduction:** Improving our understanding of outbreaks due to antibiotic-resistant bacteria (ARB) and their control is critical in the current public health scenario. The threat of outbreaks due to ARB requires multifaceted efforts. However, a global overview of epidemiological characteristics of outbreaks due to ARB and effective infection control measures is missing. In this paper, we describe the protocol of a systematic review aimed at mapping and characterising the epidemiological aspects of outbreaks due to ARB and infection control measures in European countries.

**Methods and analysis:** The databases MEDLINE, Web of Knowledge and Cochrane library will be searched using a 3-step search strategy. Selection of articles for inclusion will be performed by 2 reviewers using predefined eligibility criteria. All study designs will be included if they report an outbreak and define the microbiological methods used for microorganism identification. The target bacteria will be methicillin-resistant and vancomycin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, ceftazidime-resistant and carbapenem-resistant *Acinetobacter baumannii*, ceftazidime-resistant and carbapenem-resistant *Pseudomonas aeruginosa*, ciprofloxacin-resistant *Escherichia coli*, extended-spectrum β-lactamase-producing *E. coli* and *Klebsiella pneumoniae*, carbapenem-resistant and carbapenamase-producing *Enterobacteriaceae*. Data will be extracted using a tailored pilot tested form and the quality of reporting will be assessed using the ORION (Outbreak Reports and Intervention Studies Of Nosocomial infections) tool. Data will be synthesised and reported by the type of ARB, setting and country. Infection control measures and bundles of measures will be described. The effectiveness will be reported as defined by the authors. Regression analysis will be used to define independent factors associated with outbreaks' control. Heterogeneity between studies will be assessed by forest plots and $I^2$ statistics.

**Ethics and dissemination:** Ethical approval is not applicable for this study. Findings will be disseminated through journal publication and conference presentations and talks.

## Strengths and limitations of this study

- Our systematic review will provide a global epidemiological overview of published outbreaks due to antibiotic-resistant bacteria (ARB) and infection control measures implemented to control the ARB outbreak.
- No restriction of languages and settings (healthcare and community) will be applied.
- Multiple literature databases and publically accessible national/international surveillance systems will be searched for outbreaks due to target ARB.
- Strong under-reporting of outbreaks is expected and could limit the generalisability of results.
- Implemented infection control measures could be difficult to evaluate due to heterogeneity of national guidance documents.

## INTRODUCTION

The genetic capabilities of bacteria and indiscriminate use of antibiotics have resulted in the wide-spread development of resistance, hindering the effectiveness of antibiotic therapy.[1–5] Notably, resistance to single antibiotic has further progressed into multidrug resistance which advantageously protects bacterial pathogens against several commonly used therapeutic agents. Multidrug resistances are rapidly evolving in several bacterial species: most predominant and difficult-to-deal-with multidrug-resistant (MDR) organisms include methicillin-resistant *Staphylococcus aureus* (MRSA); vancomycin-resistant enterococci (VRE); extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli*; and MDR-*Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae*.[6–9]

In the 2011–2012 point-prevalence survey conducted by the European Centre for Disease Prevention and Control (ECDC), methicillin resistance was reported in 41% of invasive *S. aureus* isolates; vancomycin

resistance in 10% of enterococci isolates; third-generation cephalosporin resistance in 33% of all *Enterobacteriaceae* isolates; and carbapenem resistance in 8% of *Enterobacteriaceae*, 32% of *P. aeruginosa* and 81% of *A. baumannii* isolates.[10] Mortality from antimicrobial resistance was estimated at 50 000 deaths per year in the USA and Europe alone.[11] Annual worldwide mortality from antimicrobial resistance may exceed 700 000 and has been projected to rise to 10 million by 2020, a burden larger than that projected for neoplastic diseases.[12]

A well-recognised tool in the strategy to contain antibiotic resistance is surveillance.[13–16] Based on the information gathered, surveillance data on antimicrobial resistance drive clinical decision-making on empiric therapy and infection prevention policy.[17] Overall, surveillance enables improved patient outcome at the local level, while guiding public health policymaking and interventions at the national level, and helps identify emerging threats on a global scale.[18]

Under the Innovative Medicines Initiative (IMI)-funded New Drugs for Bad Bugs (ND4BB) programme, the Combating Bacterial Resistance in Europe—Molecules against Gram Negative Infections (COMBACTE-MAGNET) consortium is currently working on an unprecedented collaboration called EPI-Net (the Epidemiology Network) among representative stakeholders, experts and industry from major European countries. EPI-Net's objective is to address the limitations of current healthcare-associated and antibiotic-resistant infections surveillance within Europe.[19 20] As part of this effort and in collaboration with the DRIVE-AB consortium (IMI COMBACTE Project) a systematic review of the literature on outbreak reports, named EMBARGO (EpideMiology and control measures of outBreaks due to Antibiotic-Resistant orGanisms in EurOpe), is planned. The objective of the study will be to:

- Systematically review articles reporting outbreaks due to antibiotic-resistant bacteria (ARB) in Europe to map and describe the epidemiological characteristics of the outbreaks and infection control measures.
- Analyse effectiveness of infection control measures or bundles of measures to control the outbreaks.
- Assess quality of outbreak studies.

We report here the protocol.

## METHODS AND ANALYSIS

### Study design

A systematic review of the literature and a meta-analysis (when possible) in accordance with PRISMA statement[21] will be performed in order to identify most effective infection control measures or bundles of measures to reduce or prevent the spread of ARB.

### Inclusion criteria

The study must report an outbreak of target ARB and standard laboratory techniques for detection of microorganisms. An outbreak will be defined as an unusual or unexpected increase of cases of infection due to target ARB with or without molecular analysis of the strain.[22] The target ARB will be: MRSA, vancomycin-resistant *S. aureus*, VRE, ceftazidime-resistant and carbapenem-resistant *A. baumannii*, ceftazidime-resistant and carbapenem-resistant *P. aeruginosa*, ciprofloxacin-resistant *E. coli*, ESBL-producing *E. coli* and *K. pneumoniae*, carbapenem-resistant and carbapenamase-producing *Enterobacteriaceae*. Since the definition of an ESBL producer has changed over time,[23 24] the following definitions for ESBL will be included: (1) resistant to ceftazidime and/or ceftriaxone (the two may have different detection at different locations and may have changed over time), (2) phenotypic confirmation (eg, using β-lactamase inhibitor combination), and (3) gene identification (likely to exist initially only in single isolates, and recently for larger number of strains). Carbapenem resistance will be reported according to authors' definitions. European Committee on Antimicrobial Susceptibility Testing (EUCAST) or Clinical and Laboratory Standards Institute (CLSI) clinical breakpoints will be reported, when available. All settings (community and healthcare facilities) and all population groups (elderly, children, immunocompromised, etc), regardless of age, racial and ethnic backgrounds will be considered.

### Search strategy

We will identify all published literature reporting outbreaks due to target ARB and include all European studies reporting outbreaks. Publications will be searched through a systematic search of MEDLINE, Web of Knowledge and Cochrane library using the following terms: name of target ARB combined with 'outbreak OR outbreaks OR pandemic OR pandemics OR epidemic OR epidemics OR infectious disease outbreak OR infectious disease outbreaks OR disease outbreak OR disease outbreaks OR emergence'. Searches will be limited to 31.05.2016 ('0001/01/01'[PDat]: '2016/05/31'[PDat]; see online supplementary material 1).

A three-step search strategy will be used: (1) text words contained in the title, abstract and the index (MeSH) terms in MEDLINE; (2) keywords and index terms across all other included databases; and (3) reference list of all retrieved articles for other potentially relevant studies. No language restriction will be applied. In countries with mandatory reporting of outbreaks due to the target ARB, publicly available databases will also be included. Experts in surveillance will be contacted for unpublished data on local outbreaks.

### Selection process

A two-step selection process will be performed by two independent reviewers. Titles and abstracts of the retrieved articles will be initially screened and non-relevant studies will be excluded. The reasons for exclusion will be noted. For potentially eligible studies, the full text will then be obtained and assessed for relevance

and duplication against the predefined selection criteria.

### Data extraction process and management

All published articles obtained based on the literature search will be downloaded into a reference management database and used to document further screening. Data extraction from the included articles will be carried out and managed using Epi Info V.7.0 (CDC). Two independent reviewers will extract data using a standardised data extraction form which will be first pilot tested on a representative sample of articles. We will cross verify data and any discrepancies and inconsistencies will be discussed and sorted out by consensus.

The following data will be extracted: article-related variables: author, contact details of the corresponding author, institute, country, year of publication, year of outbreak, title of the article, journal; study-associated variables: data collection period, study design, sampling, study setting (hospital based, other healthcare facilities, community based), population profile; sociodemographic characteristics: age, sex; ARB-specific characteristics: identification method, colonisation/infection; outbreak-specific characteristics: type of screening (serum, throat swab, rectal swab, etc), type of infection, how the outbreak was detected (routine surveillance, reported by general practitioners, etc), number of patients screened; number of patients tested positive; number of patients infected and colonised; date of sentinel case; date of intervention, number of cases before the intervention, date of last case, endemicity, duration of outbreak, country and city/region of the outbreak, any mode of spread reported, clonality (clonal vs polyclonal/plasmid/gene spread if known); infection control measures: type of infection control measures, audit, duration of implementation, bundles, feedback. The infection control measures will include education (any educational measure implemented to control the ARB outbreak) and antimicrobial stewardship programmes (any programme aimed at improving prescription of antimicrobials implemented to control the ARB outbreak).

### Quality assessment—risk of bias in individual studies

Quality appraisal will be performed using the ORION (Outbreak Reports and Intervention Studies of Nosocomial Infections) statement which guides reporting of observational studies and outbreak reporting.[25] Two reviewers will independently assess the quality of each included study and any disagreements that arise will be resolved through discussion, or with a third reviewer.

### Data synthesis and analysis

We will synthesise data by ARB type, setting and country. Attack rates will be defined as the percentage of observed patients who were either colonised or infected by the target ARB in the overall population, while infection rates as the percentage of patients who were infected among those colonised. Attack rates and infection rates will be estimated by ARB and setting. Effectiveness of measures in controlling the outbreaks, as reported by the authors, will be analysed by single measures and by association of measures (when possible). Regression analysis will be used to define variables of success/failure of infection control measures used to control the outbreaks. Heterogeneity will be assessed through visual inspection of the forest plots to detect overlapping CIs and also by applying the $I^2$ statistics. A priori determined sources of heterogeneity will be studied using meta-regression. Epidemiological factors influencing the outbreaks to be self-limiting or persistent will be analysed using meta-regression. Results will be stratified by target ARB, country and time period. STATA statistical software (StataCorp 2015, Release 14, College Station, Texas, USA) will be used to conduct these analyses. As the systematic review aims to study the outbreaks, studying publication bias using funnel plots is not applicable. We will assess publication bias in a subset of data by external validation with surveillance data on outbreaks where outbreak reporting is mandatory and publicly available.

## DISCUSSION

This systematic review, carried out contextually to the establishment of the COMBACTE-MAGNET, EPI-Net will identify and summarise the relevant evidence on the epidemiological aspects of outbreaks due to ARB and effectiveness of infection control measures in reducing and/or controlling the spread of ARB in healthcare and community settings.

Strengths (ie, inclusion of unpublished data, huge sample size and regression analysis) and limitations (high heterogeneity of settings, country public health indications, mandatory reporting, laboratory facilities, different ARB transmission modalities and publication bias) of the review will be discussed and gaps in the evidence will also be highlighted. The findings of this review and those of other similar reviews will be compared (if identified) for the degree of consistency.

The evaluation of the quality of the studies will help in defining grey areas of the literature and outbreaks data reporting. Analysis of effectiveness of infection control measures could help future guidance documents in streamlining indications on outbreak control according to the type of ARB and setting and suggest areas for future studies.

## ETHICS AND DISSEMINATION

Since only published data will be used for the study, no formal ethical approval is required. The systematic review will be submitted for publication. The results of the review and data will be presented in conferences and general meetings with internal and external stakeholders, and will also be discussed with policymakers for the common purpose of developing a framework of what constitutes responsible use of existing and new antibiotics.

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**Contributors** ET, YC and FS conceptualised the study idea, oversaw the development of the protocol and prepared draft versions of the paper. BPG wrote the protocol and prepared draft versions of the manuscript. AV, JR-B, PG, FRB and NBR critically appraised the protocol and were involved to its development by revising different versions. All authors approved the final version of the protocol and take responsibility for its content.

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**Competing interests** FS is an employee of AstraZeneca, an EFPIA (European Federation of Pharmaceutical Industries and Association) member company in the IMI JU and costs related to his research contributions were covered by AstraZeneca as in-kind contribution under the IMI JU agreement.

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