

STUDY PROTOCOL

# Clinical Impact of Antimicrobial Resistance in Hospitalized Patients: a Systematic Review

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## **Background**

Accurate and reliable predictions of the burden of ARO (Antimicrobial resistant Organisms) and emerging multidrug-resistant pathogens are required to estimate antimicrobial resistance's current and future impact on society's healthcare systems and economies, and to determine future public health needs.

## **Objectives**

The overall aim is to assess the clinical impact of infections due to antimicrobial resistant strains in hospitalised patients and to create a database to inform the development of mathematical prediction models of impact of these multi drug resistant pathogens. The primary objective is to assess and estimate the clinical impact of ARO with respect to the clinical outcomes including mortality, length of hospital stay and cost in patients with infections.

Target ARO are: methicillin resistant *Staphylococcus aureus*, vancomycin resistant *Staphylococcus aureus*, vancomycin resistant *Enterococcus faecalis*, vancomycin resistant *Enterococcus faecium*, ciprofloxacin resistant *E. coli*, EBSL (Extended Spectrum beta lactamase) producing *E. coli*, carbapenem resistant / carbapenemase producing *E. coli* and *Klebsiella pneumoniae*, carbapenem resistant / carbapenemase producing *Acinetobacter baumannii*, carbapenem resistant / carbapenemase producing *Pseudomonas aeruginosa*, ceftazidime resistant *Acinetobacter baumannii*, ceftazidime resistant *Pseudomonas aeruginosa*

## **Methods**

### **Types of studies:**

All articles based on primary data on infections due to the target ARO either using interventional or observational designs reporting any clinical impact measure would be included. Epidemiological studies as well as interventional studies, surveillance reports and field reports would contribute towards this review. The review would include

studies comparing the clinical impact of infections due to ARO to those due to sensitive bacteria or randomised patients without infections.

**Study setting:**

Observational and interventional studies from all inpatient settings: clinic, hospitals, health care facilities and in all kinds of population groups: all patient groups, elderly, immuno-compromised, children, etc.

**Types of participants:**

Our review will include all studies that measured pre-selected clinical outcomes among hospitalised patients with blood stream infections, ventilator associated infections, health-care associated pneumonia, wound infections and urinary tract infections.

**Study outcomes of interest:**

Primary outcomes of interest are

- Mortality rate (all-cause mortality, attributable mortality, 30-day mortality, intensive care mortality)
- Length of stay (in hospital/ICU/post-infection)
- Cost

**Search strategies for identification of studies:**

The search strategy is developed using the name of the ARO to identify all the reports relevant to a specific ARO. These reports would be screened to identify articles describing the clinical impact using search terms related to each predetermined clinical outcome. Any important relevant clinical outcome found in the articles but not listed in the protocol would be added and analysed in secondary analyses. A three-step search strategy will be utilized in this review. An initial search of text words contained in the title, abstract and the index (MESH) terms in PubMed. A second search using all identified keywords and index terms will then be undertaken across all other included databases. Thirdly, the reference list of all identified reports and articles will be

searched for additional studies. Studies published in any language will be considered for inclusion in this review.

Additionally, previous systematic reviews relevant to our objectives would be identified and the included articles in these reviews were updated till the end of 2015 and included as well. The time window of search for each ARO would be from the initial report till the end of 2015.

The databases to be searched include:

- MEDLINE, 1950-, In-Process and other non-indexed citations, OvidSP

### **Search terms:**

The search term built for the specific AROs will be coupled with the following terms to be able to find all the relevant articles:

- (*length of stay*[mesh] OR (*hospitalisation*[tw] AND *length*[tw])) OR *length of hospitalisation*[tw] OR *length of hospitalization*[tw] OR *duration of hospitalization*[tw] OR *duration of hospitalisation*[tw] OR *LOS*[tw] OR ((*period*[tw] OR *length*[tw]) AND (*hospital stay*[tw] OR *hospitalisation*[tw] OR *hospitalization*[tw])) OR
- (*mortality*[mesh] OR *mortality*[tw] OR *death rate*[tw] OR *fatality*[tw] OR *survival rate*[tw] OR *death*[tw] OR *died*[tw] OR *dead*[tw])) OR
- (*cost*\*[Title/Abstract] OR "costs and cost analysis"[MeSH:noexp])

Coupled with

- (((("Methicillin resistant"[tw] OR "Methicillin resistance"[tw] OR "Methicillin resistant"[MeSH] OR "Methicillin resistance"[MeSH] OR "Meticillin resistant"[tw] OR "Meticillin resistance"[tw] OR "Meticillin resistant"[MeSH] OR "Meticillin resistance"[MeSH] OR "Meticillin-resistant"[MeSH] OR "Meticillin-resistance"[MeSH] OR "Methicillin-resistant"[MeSH] OR "Methicillin-resistance"[MeSH] OR "Meticillin-resistant"[tw] OR "Meticillin-resistance"[tw] OR "Methicillin-resistant"[tw] OR "Methicillin-resistance"[tw] OR "MRSA"[tw] OR "MRSA"[MeSH] ))) AND (*Staphylococcus aureus* [Mesh] OR *Staphylococcus aureus* [tw] OR *S.aureus*[Mesh] OR *S.aureus*[tw])))
- (("""vancomycin resistant""""[tw] OR """"Vancomycin resistance""""[tw] OR """"vancomycin resistant""""[MeSH] OR """"Vancomycin resistance""""[MeSH] OR *vancomycin-resistan*\*[mesh] OR *vancomycin-resistan*\*[tw] )) OR ((*Drug resistance*,

*Microbial [Mesh] AND Vancomycin/Pharmacology)))) AND ((Staphylococcus aureus[Mesh] OR Staphylococcus aureus[tw] OR S.aureus[Mesh] OR S.aureus[tw])*

- *""""vancomycin resistant""""[tw] OR """"Vancomycin resistance""""[tw] OR """"vancomycin resistant""""[MeSH] OR """"Vancomycin resistance""""[MeSH] OR Vancomycin-resistan\*[tw] OR vancomycin-resistan\*[MeSH])) OR ((Drug resistance, Microbial [Mesh] AND Vancomycin/Pharmacology)))) AND (((("Enterococcus faecalis""[tw] OR """"Enterococcus""""[tw] OR """"Enterococcus faecium""""[tw] OR """"Enterococci""""[tw] OR """"Enterococcal""""[tw] OR """"Enterococcus faecalis""""[MeSH] OR """"Enterococcus""""[MeSH] OR """"Enterococcus faecium""""[MeSH] OR """"Enterococci""""[MeSH] OR """"Enterococcal""""[MeSH])) OR ((group D streptococc\*[tw]))*
- *((ceftazidime[mesh] OR ceftazidime[tw]) AND (Drug resistance[Mesh] OR resistan\*[tw]) AND (""""Acinetobacter baumannii""""[MeSH Terms] OR """"Acinetobacter baumannii""""[tw] OR """"A.baumannii""""[tw] OR """"Acinetobacter baumannii""""[MeSH Terms] OR """"Acinetobacter baumannii""""[tw] OR """"A.baumannii""""[tw] OR """"Pseudomonas aeruginosa""""[MeSH Terms] OR """"Pseudomonas aeruginosa""""[tw] OR """"P.aeruginosa""""[tw] OR """"P.aeruginosa""""[Mesh]))*
- *((ciprofloxacin[mesh] OR ciprofloxacin[tw] OR cipro[tw] ) AND (Drug resistance[Mesh] OR resistan\*[tw])) AND ((Escherichia Coli[Mesh] OR E.coli[Mesh] OR Escherichia Coli[tw] OR E.coli[tw])*
- *((ESBL[tw] OR ""Extended spectrum beta-lactamase""[tw] OR ESBL[Mesh] OR ""Extended spectrum beta-lactamase"" [Mesh]) OR Extended spectrum ? lactamase[tw] OR Extended spectrum ? lactamase[Mesh] ) AND (Escherichia Coli[Mesh] OR E.coli[Mesh] OR Escherichia Coli[tw] OR E.coli[tw])*
- *((ESBL[tw] OR ""Extended spectrum beta-lactamase""[tw] OR ESBL[Mesh] OR ""Extended spectrum beta-lactamase"" [Mesh]) OR Extended spectrum ? lactamase[tw] OR Extended spectrum ? lactamase[Mesh] ) AND (Klebsiella pneumoniae[Mesh] OR K.Pneumoniae[Mesh] OR Klebsiella pneumoniae[tw] OR K.Pneumoniae[tw])*
- *(((((carbapenem[mesh] OR carbapenem[tw] OR carbapenemase[Mesh] OR carbapenemase[tw] )) AND (Drug resistance[Mesh] OR resistan\*[tw])) AND (Drug resistance[Mesh] OR resistan\*[tw]) AND ((Klebsiella pneumoniae[Mesh] OR K.Pneumoniae[Mesh] OR Klebsiella pneumoniae[tw] OR K.Pneumoniae[tw])) OR (((("Pseudomonas aeruginosa""""[MeSH Terms] OR """"Pseudomonas aeruginosa""""[tw] OR """"P.aeruginosa""""[tw] OR """"P.aeruginosa""""[Mesh])))))) OR (Drug resistance[Mesh] OR resistan\*[tw])*

*AND (Escherichia Coli[Mesh] OR E.coli[Mesh] OR Escherichia Coli[tw] OR E.coli[tw]) OR (((("Acinetobacter baumannii"[MeSH Terms] OR "Acinetobacter baumannii"[tw] OR "A.baumannii"[tw] OR "Acinetobacter baumannii"[MeSH Terms] OR "Acinetobacter baumannii"[tw]) OR "A.baumannii"[tw]))))*

## **Data collection and analysis**

### **Inclusion and exclusion criteria:**

Published studies on human subjects would be included in accordance with the objective of the review.

#### **Inclusion criteria:**

1. Published studies on human subjects studying ARO of interest.
2. Reporting at least one of the outcome measures: mortality, length of hospital stay, cost
3. Presence of a comparison group - the comparison group could be either patients with infections due to sensitive bacteria or randomised patients without infections.

#### **Exclusion criteria:**

1. Studies looking at colonisations only.
2. Diagnostic studies, reviews and non-clinical studies.
3. Study protocols.

Abstracts presented at conferences would not be included. Studies on patients with colonization alone would be excluded.

### **Selection of studies:**

Eligibility of the resulting articles from the initial search based on title and abstract screening would be assessed by two reviewers and discrepancies sorted out. The reasons for exclusion of articles would be noted down. The researchers will not be blinded to study authors or location.

### **Data extraction and management:**

The full text of the resulting eligible articles would be carefully read through to extract and enter the data onto a standardised pre-formatted data sheet by two reviewers. The databases would be cross verified to find any discrepancies and inconsistencies will be discussed among the study team and sorted out by consensus. All major decisions will be documented and difference of opinion within the research team regarding the extracted variables will be resolved by discussion with the senior researcher. Authors will be contacted to enquire regarding missing data.

The data to be extracted are:

Article related variables:

- Name of the author
- Email of the corresponding author,
- Institute
- Country and year of publication
- Title of the article
- Journal

Study population related general variables:

- Time of data collection
- Study setting (hospital based, other health care facilities)
- Population profile (Immuno-compromised, elderly, children, etc)

Study design related variables:

- Type of study design
- Comparison group used
- Number of patients in each arm who completed follow-up

ARO specific characteristics:

- Name of the ARO
- Type of infection
- Site of infection

Outcome reported:

- Name of the outcome measure (e.g. mortality rate)
- Definition of the outcome measure
- Value of the outcome measure for both the arms

- Unadjusted value of the effect measure (e.g. odds ratio of mortality among MRSA vs MSSA)
- Adjusted value of the effect measure
- Adjusting variables

For each outcome, the values for both the arms and its precision measures (sd, SE, 95%CI, etc), the number of patients who contributed to the measurement. If there is no SE estimate, sd in case of continuous variable and numerator and denominator values for the binary outcome.

### **Data synthesis and analysis:**

The database would be synthesized separately for each ARO for various types of infections. We will visually inspect the forest plots as well as assess the heterogeneity within various factors with the help of I-square measure and its confidence interval. The clinical impact would be studied using odds ratio as the effect measure and wherever relevant, an overall estimate of the clinical impact would be obtained based on a random effects model. Sources of heterogeneity determined apriori would be studied using meta-regression. Epidemiological factors influencing the clinical impact would be studied as well using meta-regression.

### **Assessment of risk of bias in the included studies**

The quality of the eligible trials will be assessed by two researchers independently. If any disagreement occurs, it will be resolved by discussion and consensus. EPOC assessment criteria for RCTs, NewCastle Ottawa quality assessment scale for case control studies and cohort studies were modified and used.

For RCTs the quality criteria assessed will be:

- Generation of allocation sequence adequate? (Yes/No/Unclear)
- Allocation concealment adequate? (Yes/No/Unclear)
- Validated and reliable primary outcome measures/systems are used? (Yes/No/Unclear)
- Baseline/primary outcome measurements similar? (Yes/No/Unclear)
- Baseline/primary characteristics similar? (Yes/No/Unclear)
- Adequate addressing of incomplete data outcome? (Yes/No/Unclear)
- Blinding to primary outcome achieved? (Yes/No/Unclear)



- Adequate protection against contamination? (Yes/No/Unclear)

For Case Control studies, the quality criteria assessed will be:

- Is the case definition adequate? (yes, no, unclear)
- Representativeness of the cases (consecutive or obviously representative series of cases, potential for selection biases or not stated)
- Selection of Controls (community controls, hospital controls ,no description)
- Definition of Controls (no history of disease (endpoint), no description of source)
- study controls for the most important factor (yes, no, unclear)
- study controls for any additional factor (yes, no, unclear)
- Ascertainment of exposure (secure record (eg surgical records), structured interview where blind to case/control status, interview not blinded to case/control status, written self report or medical record only, no description)
- Same method of ascertainment for cases and controls\_(Yes/No/Unclear)
- Non-Response rate (same rate, non respondents described, rate different and no designation)

For cohort studies, the quality criteria assessed will be:

- Representativeness of the exposed cohort (truly representative, somewhat representative , selected group of users, no description)
- Selection of the non exposed cohort (drawn from the same community as the exposed cohort, drawn from a different source, no description of the derivation of the non exposed cohort)
- Ascertainment of exposure (secure record (eg surgical records), structured interview, written self report, no description)
- Demonstration that outcome of interest was not present at start of study(Yes/No/Unclear)
- Comparability of cohorts on the basis of the design or analysis (study controls for the most important factor, study controls for any additional factor)
- Assessment of outcome (independent blind assessment, record linkage, self report, no description)
- Follow-up long enough for outcomes to occur (Yes/No/Unclear)
- Adequacy of follow up of cohorts ( complete follow up – all that matters subjects accounted for, subjects lost to follow up unlikely to introduce bias - small number, inadequate numbers but description provided of those lost, inadequate follow up rate and no description of those lost, no statement).