

# THE LANCET

## Infectious Diseases

### Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Cassini A, Högberg LD, Plachouras D, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis* 2018; published online Nov 5. [http://dx.doi.org/10.1016/S1473-3099\(18\)30605-4](http://dx.doi.org/10.1016/S1473-3099(18)30605-4).



## Burden of antimicrobial resistance

Appendix to

“Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the European Union and the European Economic Area in 2015: a population-level health estimate”

# Contents

|   |     |
|---|-----|
| Literature review report .....  | 3   |
| Literature selection grids.....   | 142 |
| Final disease outcome trees.....  | 168 |
| Methodology protocol to estimate incidence.....   | 191 |
| GATHER checklist and further analysis on MRSA and attribution as<br>healthcare-associated infections..... | 213 |
| Country specific results.....   | 223 |

## Burden of antimicrobial resistance

# Literature review report

Literature search undergone by Ana Hoxha and Victoria Simpkin

Report written by Ana Hoxha and Alessandro Cassini with contributions from Carl Suetens, Liselotte Diaz Högberg, Diamantis Plachouras and Dominique Monnet

# Contents

|  |     |
|--|-----|
| List of abbreviations .....  | 5   |
| Introduction .....   | 6   |
| Methodology.....   | 6   |
| PICO Questions.....  | 7   |
| PRISMA Checklist .....   | 9   |
| Results .....  | 14  |
| 1. Carbapenem resistant <i>Acinetobacter baumannii</i> .....                   | 14  |
| 2. Colistin resistant <i>Acinetobacter baumannii</i> .....                     | 21  |
| 3. Multidrug resistant <i>Acinetobacter baumannii</i> .....                    | 24  |
| 4. Carbapenem resistant <i>Escherichia coli</i> .....                          | 31  |
| 5. Colistin resistant <i>Escherichia coli</i> .....                            | 35  |
| 6. Third-generation Cephalosporin resistant <i>Escherichia coli</i> .....      | 38  |
| 7. Carbapenem resistant <i>Klebsiella pneumoniae</i> .....                     | 47  |
| 8. Colistin resistant <i>Klebsiella pneumoniae</i> .....                       | 55  |
| 9. Third-generation Cephalosporin resistant <i>Klebsiella pneumoniae</i> ..... | 58  |
| 10. Methicillin resistant <i>Staphylococcus aureus</i> .....                   | 66  |
| 11. Carbapenem resistant <i>Pseudomonas aeruginosa</i> .....                   | 86  |
| 12. Colistin resistant <i>Pseudomonas aeruginosa</i> .....                     | 92  |
| 13. Multidrug resistant <i>Pseudomonas aeruginosa</i> .....                    | 94  |
| 14. Penicillin resistant <i>Streptococcus pneumoniae</i> .....                 | 101 |
| 15. Penicillin and macrolide resistant <i>Streptococcus pneumoniae</i> .....   | 106 |
| 16. Vancomycin resistant <i>Enterococcus faecalis</i> and <i>faecium</i> ..... | 107 |
| Conclusions .....  | 116 |
| References .....   | 118 |

## List of abbreviations

|          |   |
|----------|---|
| 3GCREC   | third-generation cephalosporin-resistant <i>E. coli</i>   |
| 3GCRKP   | third-generation cephalosporin-resistant <i>K. pneumoniae</i>   |
| AMR      | antimicrobial resistance  |
| BSI      | bloodstream infection   |
| CAI      | Community-associated infections   |
| CI       | confidence interval   |
| CoIRACI  | colistin-resistant <i>Acinetobacter</i> spp.  |
| CoIREC   | colistin-resistant <i>E. coli</i>   |
| CoIRKP   | colistin-resistant <i>K. pneumoniae</i>   |
| CoIRPA   | colistin-resistant <i>P. aeruginosa</i>   |
| CRACI    | carbapenem-resistant <i>Acinetobacter</i> spp.  |
| CREC     | carbapenem-resistant <i>E. coli</i>   |
| CRKP     | carbapenem-resistant <i>K. pneumoniae</i>   |
| CRPA     | carbapenem-resistant <i>P. aeruginosa</i>   |
| CSF      | cerebral spine fluid  |
| DALY     | disability-adjusted life years  |
| EARS-Net | European Antimicrobial Resistance Surveillance Network  |
| EEA      | European Economic Area  |
| EU       | European Union  |
| HAI      | healthcare-associated infection   |
| LOS      | length of stay  |
| MDR      | multidrug-resistant   |
| MDRACI   | multidrug-resistant <i>Acinetobacter</i> spp  |
| MDRPA    | multidrug-resistant <i>P. aeruginosa</i>  |
| MRSA     | meticillin-resistant <i>Staphylococcus aureus</i>   |
| MS       | Member State  |
| NI       | Non infected  |
| OECD     | Organisation for Economic Co-operation and Development  |
| OTH      | other infection site including digestive tract infections, skin and soft tissue infections (SSTI), eye, ear, nose or mouth infections, bone and joint infections, cardiovascular infections, reproductive tract infections and other less frequent infections |
| PMRSP    | penicillin- and macrolide-resistant <i>S. pneumoniae</i>  |
| PPS      | point prevalence survey of healthcare-associated infections and antimicrobial use in acute care hospitals   |
| PRSP     | penicillin-resistant <i>S. pneumoniae</i> ;   |
| R        | Resistant   |
| RESP     | respiratory infections (including pneumonia, and low respiratory tract infection)   |
| S        | Susceptible   |
| S-BSI    | secondary BSI   |
| SP       | specified pathogens   |
| SPDAR    | specified pathogens with defined antimicrobial resistance   |
| SSI      | surgical site infection   |
| UTI      | urinary tract infection   |
| VRE      | vancomycin-resistant enterococci  |

## Introduction

This document is part of the burden of antibiotic resistance in Europe project. The objective of this research was to retrieve available evidence from peer-reviewed publications on the attributable case fatality and attributable length of stay (LOS) of resistant bacteria under surveillance by the European Antimicrobial Resistance Surveillance Network (EARS-Net) and as defined in the Supplementary appendix 4. The aim of the review is to provide information for relevant disease progression models.

## Methodology

The bacteria included in the review were the followings; *Acinetobacter baumannii*, *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Enterococcus faecalis* and *Enterococcus faecium*. For each of these bacteria we performed separate reviews to study the resistance to specific antibiotics or specific antibiotic class. The following literature reviews were performed:

1. Colistin Resistant *Acinetobacter baumannii*
2. Carbapenem Resistant *Acinetobacter baumannii*
3. Multidrug resistant *Acinetobacter baumannii*
4. Colistin Resistant *Escherichia coli*
5. Carbapenem Resistant *Escherichia coli*
6. Third-generation Cephalosporin Resistant *Escherichia coli*
7. Colistin Resistant *Klebsiella pneumoniae*
8. Carbapenem Resistant *Klebsiella pneumoniae*
9. Third-generation Cephalosporin Resistant *Klebsiella pneumoniae*
10. Meticillin-resistant *Staphylococcus aureus*
11. Colistin Resistant *Pseudomonas aeruginosa*
12. Carbapenem Resistant *Pseudomonas aeruginosa*
13. Multidrug resistant *Pseudomonas aeruginosa*
14. Penicillin resistant *Streptococcus pneumoniae*
15. Penicillin and macrolide resistant *Streptococcus pneumoniae*
16. Vancomycin resistant *Enterococcus faecalis* and *faecium*

The databases used for the literature review were PubMed, EMBASE and Cochrane Database of Systematic Reviews. Each review was performed using specific key words; research filters were applied where specified below. No time filter was applied, except for meticillin-resistant *Staphylococcus aureus* (MRSA), see below. Searches were undergone between April 2016 and December 2016, articles published after these dates might not be included.

Most studies identified were based on hospitalized populations. Therefore, we define as “attributable” the quantitative information below on mortality and/or case fatality (CF) and/or length of stay (LOS) as being attributable to the infection, factoring out the risk resulting from the underlying co-morbidity. This attributable risk (risk difference) is the comparison of the absolute risks between patients with the respective resistant (R) infection

and patients (with similar characteristics) without the infection (non-infected, NI) or infected with a susceptible (S) infection.

Primary studies reporting original results were considered eligible. Existing systematic reviews and meta-analysis were also included

To be eligible, a study had to fulfil the following inclusion criteria defined a priori:

1. Original study reporting mortality rates, attributable mortality data, case fatality rates, attributable case fatality data.
2. Original study reporting length of stay in hospital or/and attributable length of stay as compared to controls.
3. Include a control group defined as affected by a susceptible infection or/and a control group of not infected patients.

Relevant data were extracted, collected in excel spread sheets and presented in the relevant tables below.

Matched case-control or cohort studies were considered having a higher value of evidence, though we did not apply any evaluation criteria to the included studies.

Studies focusing on specific sites of infection (e.g. blood stream infections) were prioritized, although studies not specifying the infection site were also included and the data extracted.

Case report studies and articles with less than 5 case patients were excluded.

Most eligible studies reported an infected case group and a control group. The latter could be represented by non-infected (NI) patients or patients reporting an infection susceptible (S) to the considered antibiotic/class of antibiotics.

## PICO Questions

**Research question:** What is the attributable mortality and the attributable length of stay of patients with infections with antibiotic-resistant bacteria when compared with non-infected or susceptible infection?

|  |  |
|--|--|
| <b>P</b> opulation<br>Patients with defined infections with antibiotic-resistant bacteria, stratified for age group and infection type/site. | <b>I</b> ntervention (exposure)<br>Infection due to: <ul style="list-style-type: none"><li>– Colistin Resistant <i>Acinetobacter baumannii</i></li><li>– Carbapenem Resistant <i>Acinetobacter baumannii</i></li><li>– Multidrug resistant <i>Acinetobacter baumannii</i></li><li>– Colistin Resistant <i>Escherichia coli</i></li><li>– Carbapenem Resistant <i>Escherichia coli</i></li><li>– Third-generation Cephalosporin Resistant <i>Escherichia coli</i></li><li>– Colistin Resistant <i>Klebsiella pneumoniae</i></li><li>– Carbapenem Resistant <i>Klebsiella pneumoniae</i></li></ul> |
|--|--|



|   |   |
|---|---|
|   | <ul style="list-style-type: none"> <li>– Third-generation Cephalosporin Resistant <i>Klebsiella pneumoniae</i></li> <li>– Methicillin-resistant <i>Staphylococcus aureus</i></li> <li>– Colistin Resistant <i>Pseudomonas aeruginosa</i></li> <li>– Carbapenem Resistant <i>Pseudomonas aeruginosa</i></li> <li>– Multidrug resistant <i>Pseudomonas aeruginosa</i></li> <li>– Penicillin resistant <i>Streptococcus pneumoniae</i></li> <li>– Penicillin and macrolide resistant <i>Streptococcus pneumoniae</i></li> <li>– Vancomycin resistant <i>Enterococcus faecalis</i> and <i>Enterococcus faecium</i></li> </ul> |
| <p><b>Comparison</b><br/> Non-infected patients or patients infected with susceptible strain of the same species.</p> | <p><b>Outcome</b><br/> Attributable case fatality and attributable length of stay.</p>  |

## PRISMA Checklist

| Section/topic      | # | Checklist item  |
|--------------------|---|---|
| <b>TITLE</b>       |   |   |
| Title              | 1 | Burden of infections with antibiotic resistant bacteria: a systematic literature review of case fatality and length of stay   |
| <b>ABSTRACT</b>    |   |   |
| Structured summary | 2 | <p><b>Background and Objectives:</b> in order to estimate the burden infections with antibiotic-resistant we built disease progression models. We performed several systematic reviews of the literature to extract the best available evidence on the attributable case fatality proportion and attributable length of stay (LOS) in order to inform the disease progression models. Separate systematic literature reviews were performed for each bacteria under surveillance by the European Antimicrobial Resistance Surveillance Network (EARS-Net), each type of resistance and each infection type/site.</p> <p><b>Data source:</b> The articles were searched on PubMed, Embase and the Cochrane Database of Systematic Reviews.</p> <p><b>Study Eligibility criteria:</b> The review included primary studies reporting case fatality rate and LOS of patients with the resistant (R) infection and patients (with similar characteristics) without the infection (non-infected, NI) or infected with a susceptible (S) strain, for each resistant bacteria and each infection type/site.</p> <p><b>Participants:</b> The cases were infected patients with a resistant infection while the controls had a susceptible or infection or were non-infected. Both groups were followed up for a period of 14-30 days measuring their mortality and LOS rates.</p> <p><b>Results:</b> The number of studies varied between the different types of resistance considered, ranging from the 0 for colistin resistant E. coli to 44 for meticillin resistant S. aureus. The information was extracted for all studies included in the review and outcomes are available in Table form.</p> <p><b>Limitations:</b> The major limitation of the review includes the heterogeneity of the studies, in terms of settings as well as type of patients and outcomes.</p> <p><b>Conclusions:</b> We found a wide difference between the studies identified in our search. Many are limited to specific healthcare services (e.g. ICUs) and/or performed on particular groups of patients (e.g. only children, only elderly) and/or with specific underlying conditions (e.g. immunodeficiency, organ transplant). Therefore, extracting valid case attributable fatality proportions and attributable LOS will be particularly challenging. Based on the heterogeneity of the studies detected, we advise to avoid pooling and averaging the results based on our categorizing criteria. We suggest an alternative method for selecting and extracting the data for the disease progression models.</p> |

| INTRODUCTION              |   |   |
|---------------------------|---|---|
| Rationale                 | 3 | In order to estimate the burden infections with antibiotic-resistant we built disease progression models. We performed several systematic reviews of the literature to extract the best available evidence on the attributable case fatality proportion and attributable length of stay (LOS) in order to inform the disease progression models. Separate systematic literature reviews were performed for each bacteria under surveillance by the European Antimicrobial Resistance Surveillance Network (EARS-Net), each type of resistance and each infection type/site.   |
| Objectives                | 4 | To identify evidence from published scientific literature on the attributable case fatality and attributable length of stay (LOS) of infections due to antibiotic-resistant bacteria under surveillance by the European Antimicrobial Resistance Surveillance Network (EARS-Net).   |
| METHODS                   |   |   |
| Protocol and registration | 5 | NA  |
| Eligibility criteria      | 6 | <p>To be eligible, a study had to fulfil the following inclusion criteria defined a priori:</p> <ul style="list-style-type: none"> <li>– Original study reporting mortality rates, attributable mortality data, case fatality rates, attributable case fatality data.</li> <li>– Original study reporting length of stay in hospital or/and attributable length of stay as compared to controls.</li> <li>– Include a control group defined as affected by a susceptible infection or/and a control group of not infected patients.</li> </ul> <p>The bacteria included in the review were the following; <i>Acinetobacter baumannii</i>, <i>Escherichia coli</i>, <i>Klebsiella pneumoniae</i>, <i>Staphylococcus aureus</i>, <i>Pseudomonas aeruginosa</i>, <i>Streptococcus pneumoniae</i>, <i>Enterococcus faecalis</i> and <i>Enterococcus faecium</i>. For each of these bacteria we performed separate reviews to study the resistance to specific antibiotics or specific antibiotic class. The following literature reviews were performed:</p> <ol style="list-style-type: none"> <li>1. Colistin Resistant <i>Acinetobacter baumannii</i></li> <li>2. Carbapenem Resistant <i>Acinetobacter baumannii</i></li> <li>3. Multidrug resistant <i>Acinetobacter baumannii</i></li> <li>4. Colistin Resistant <i>Escherichia coli</i></li> <li>5. Carbapenem Resistant <i>Escherichia coli</i></li> <li>6. Third-generation Cephalosporin Resistant <i>Escherichia coli</i></li> <li>7. Colistin Resistant <i>Klebsiella pneumoniae</i></li> <li>8. Carbapenem Resistant <i>Klebsiella pneumoniae</i></li> <li>9. Third-generation Cephalosporin Resistant <i>Klebsiella pneumoniae</i></li> <li>10. Methicillin-resistant <i>Staphylococcus aureus</i></li> </ol> |

|                         |    |  |
|-------------------------|----|--|
|                         |    | <p>11. Colistin Resistant <i>Pseudomonas aeruginosa</i><br/> 12. Carbapenem Resistant <i>Pseudomonas aeruginosa</i><br/> 13. Multidrug resistant <i>Pseudomonas aeruginosa</i><br/> 14. Penicillin resistant <i>Streptococcus pneumoniae</i><br/> 15. Penicillin and macrolide resistant <i>Streptococcus pneumoniae</i><br/> 16. Vancomycin resistant <i>Enterococcus faecalis</i> and <i>Enterococcus faecium</i></p>  |
| Information sources     | 7  | PubMed, Embase, Cochrane Database of Systematic Reviews  |
| Search                  | 8  | <p>In the different information sources, we used the following string types:<br/> PubMed: we used once the mesh term "<i>bacteria name</i>" AND all fields "<i>antibiotic name</i> resistant", and the second time the mesh term "<i>bacteria name</i>" AND all fields "<i>antibiotic name</i> resistance". Both times a filter for human studies was applied.<br/> Embase: we searched for '<i>bacteria name</i>' AND '<i>antibiotic name</i> resistant', and '<i>bacteria name</i> AND '<i>antibiotic name</i> resistance'. We applied a filter to include only human studies.<br/> Cochrane Library: we performed an advanced search using terms "<i>bacteria name</i>" AND "<i>antibiotic name</i>".</p> |
| Study selection         | 9  | All results from the three different data sources were exported in a reference manager and duplicates were removed. The first screening was performed by the articles titles, then by the abstract and finally by the evaluation of the full text.   |
| Data collection process | 10 | The data of the included studies were extracted in an excel file containing a list of indicators of interest and are displayed in Tables in the report of the systematic review and in excel files for scoring (Appendix 2).   |
| Data items              | 11 | <p>The indicators reported in the Literature review report tables (Appendix 1) include:</p> <ul style="list-style-type: none"> <li>• Author</li> <li>• Study period</li> <li>• Outcome</li> <li>• Location</li> <li>• Period of Outcome</li> <li>• Population</li> <li>• Matching criteria</li> <li>• LOS (days)</li> <li>• Notes/comments</li> </ul> <p>The indicators collected during the study evaluation (Appendix 2) were:</p>   |

|                                    |    |  |
|------------------------------------|----|--|
|                                    |    | <ul style="list-style-type: none"> <li>• First author, year</li> <li>• Study type</li> <li>• Sample size: Number cases and controls, Calculation a priori of the sample size</li> <li>• Representativeness: Geographical, Demographical, Clinical</li> <li>• Matching or controlling for confounders: Underlying disease, Infection site, Hospital and unit/ward, Follow-up</li> <li>• Risk difference: Case fatality, LOS, Statistically significant outcome results</li> </ul> |
| Risk of bias in individual studies | 12 | <p>Every indicator was scored using the following scoring scale:</p> <p>++ : Matches completely/is completely fulfilled</p> <p>+ : Matches incompletely but sufficiently/is only partly but sufficiently fulfilled</p> <p>- : Does not match or matches insufficiently/is insufficiently</p> <p>c.b.e : Cannot be evaluated</p>  |
| Summary measures                   | 13 | Attributable case fatality and attributable LOS  |
| Synthesis of results               | 14 | The results were evaluated from ECDC experts.  |
| Risk of bias across studies        | 15 | <p>Publication bias was not assessed, although some bias was expected due to the lower propensity to publish negative studies.</p> <p>Studies were conducted in different countries and different settings, making their direct comparison challenging.</p> <p>We scored each individual study for the criteria/indicators listed above (Appendix 2)</p>   |
| Additional analyses                | 16 | NA   |
| <b>RESULTS</b>                     |    |  |
| Study selection                    | 17 | The study selection process for each antibiotic resistance-bacterium combination is shown in specific Figures in Appendix 1.   |
| Study characteristics              | 18 | These are presented in Appendix 1 (Tables) and Appendix 2 (excel form).  |
| Risk of bias within studies        | 19 | These were scored according to a set criteria/indicators and the results are presented in Appendix: 2  |
| Results of individual studies      | 20 | Tables in Appendix 1 and excel in Appendix 2.  |
| Synthesis of results               | 21 | The articles included in the review were further analysed and evaluated by ECDC experts and those considered of higher quality were used as a source for the estimate of the attributable case fatality and attributable LOS, see  |

|                             |    |   |
|-----------------------------|----|---|
|                             |    | Appendix 3.<br>Appendix 3 provides an overview of the final decisions for the disease progression models.   |
| Risk of bias across studies | 22 | Very often the studies were conducted in different countries and different settings, making their direct comparison challenging. To mitigate this heterogeneity, we used the scoring system of the indicators in order to better summarise the information. Majority of studies identified were observational and carry inherent biases related to their design.  |
| Additional analysis         | 23 | NA  |
| <b>DISCUSSION</b>           |    |   |
| Summary of evidence         | 24 | The synthesized results showed an increased mortality and LOS in infected patients. For some antibiotic resistance-bacterium combinations, the resistant infection showed increased mortality and LOS compared to the susceptible infections. There was a large variation across different types of infection, bacterial species and resistant phenotypes.  |
| Limitations                 | 25 | The major limitation of the review includes the heterogeneity of the studies, in terms of study design, settings as well as type of patients and outcomes.  |
| Conclusions                 | 26 | We found a wide difference between the studies identified in our search. Many are limited to specific healthcare services (e.g. ICUs) and/or performed on particular groups of patients (e.g. only children, only elderly) and/or with specific underlying conditions (e.g. immunodeficiency, organ transplant). Therefore, extracting valid case attributable fatality proportions and attributable LOS will be particularly challenging. Based on the heterogeneity of the studies detected, we advise to avoid pooling and averaging the results based on our categorizing criteria.<br>Therefore, we chose to score the evidence identified by a self-designed evaluation grid, see Appendix 2. |
| <b>FUNDING</b>              |    |   |
| Funding                     | 27 | Funding provided by ECDC  |

## Results

The results of the reviews are presented separately for every bacteria and are antibiotic or antibiotic class specific.

Each chapter includes:

- a short description of the key words researched in every database;
- a scheme of the number of articles included and excluded during each step of the reviewing process;
- the articles selected as eligible for the review listed in separate tables based on the infection site and the comparison control group;
- some final considerations regarding the specific review.

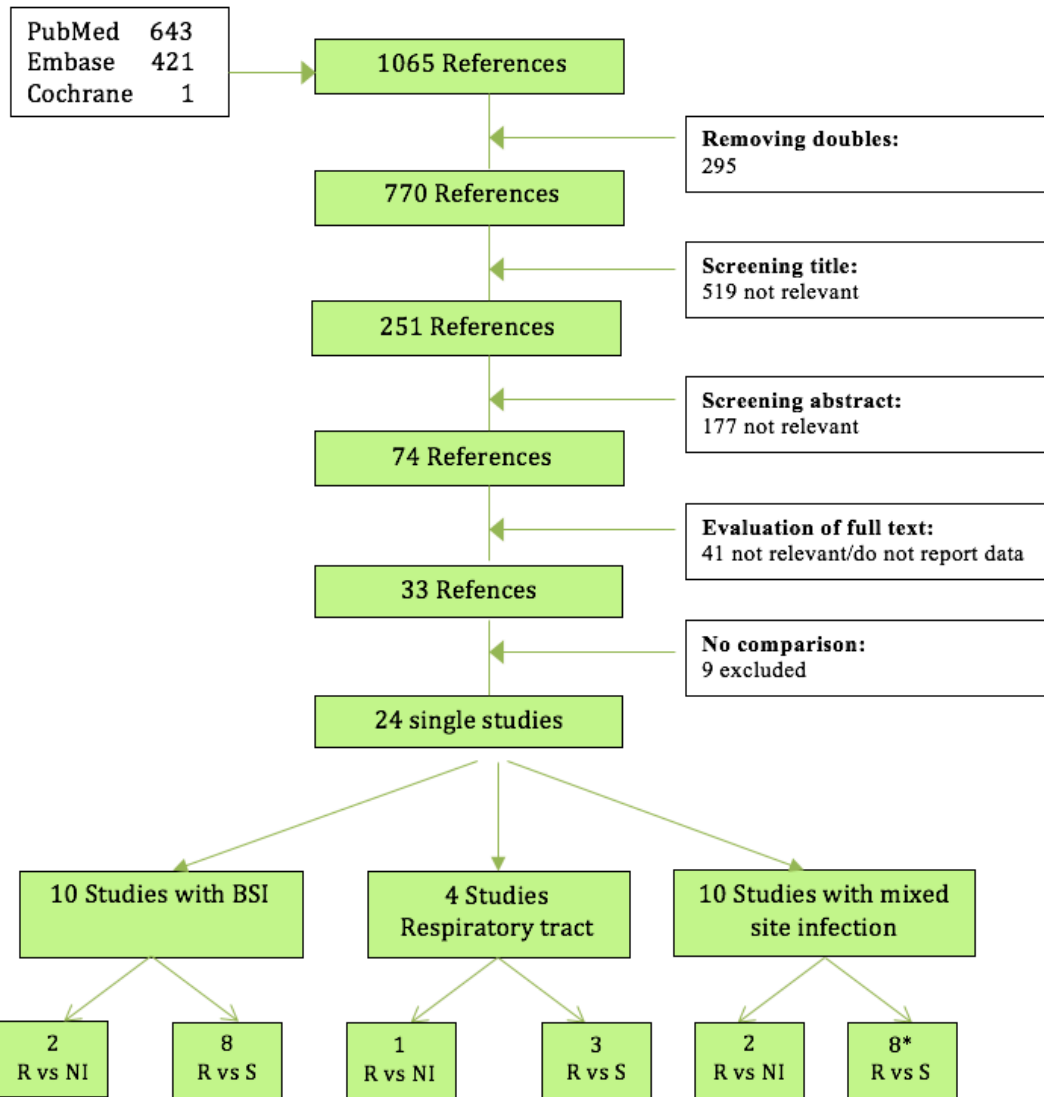
### 1. Carbapenem resistant *Acinetobacter baumannii*

To research the attributable case fatality and the attributable LOS to carbapenem resistant *Acinetobacter baumannii* (CRAB) we performed 2 advanced searches on Pubmed using once the mesh term “*Acinetobacter baumannii*” AND all fields “carbapenem resistant”, and the second time the mesh term “*Acinetobacter baumannii*” AND all fields “carbapenem resistance”. Both times a filter for human studies was applied. Embase was searched for ‘*Acinetobacter baumannii*’ AND ‘carbapenem resistant’, and ‘*Acinetobacter baumannii* AND ‘carbapenem resistance’. We applied a filter to include only human studies. An advanced search on the Cochrane Library was performed using terms “*Acinetobacter baumannii*” AND “carbapenem”. No language restrictions were made, and no further filters were applied. The flow diagram, presented in Figure 1 describes the steps in the literature review of carbapenem resistant *Acinetobacter baumannii* infections. The results obtained using the two different strings for PubMed and Embase were aggregated.

Once identified the studies reporting relevant data, these were grouped based on the site of infection.

All eligible studies reported a CRAB infected group and a control group. The latter could be represented by non-infected (NI) or carbapenem susceptible *Acinetobacter baumannii* (CSAB) infected patients.

Figure 1: Search for studies on carbapenem resistant *Acinetobacter baumannii*. Inclusion and exclusion diagram.



\* One of these studies was a systematic review and meta-analysis.

The following tables include studies reporting results for BSI, respiratory tract and for mixed site of infection due to CRAB, based on the comparison group they used. All information is reported as was presented in the original papers.

Studies that include both a susceptible and a non-infected control group, were categorized in the latter group since we prioritized the non-infected comparator.



Table 1: Short extraction table of original articles on BSI mortality of CRAB infected patients vs non infected patients

| Nr | Author                             | Study Period | Study type                       | Outcome   | Location | Period of outcome | Population                                  | Matching criteria   | LOS (days)   | Notes   |
|----|------------------------------------|--------------|----------------------------------|---|----------|-------------------|---|---------------------|--|---|
| 1  | Kim 2014 <sup>1</sup>              | 01/05-12/11  | Retrospective case-control study | Mort. rate cases=94.7%<br>Mort. rate controls=8.3%  | Korea    | hospitaliz        | 19 cases<br>38 controls                     | undelying condition | median (range)<br>cases=35(30-47)<br>controls=29(26.75-34)                         | all patients were hematopietic stem cell transplantation recipients |
| 2  | Thatrimontrichai 2013 <sup>2</sup> | 01/91-12/10  | Case-case-control study          | Mort. rate resist=42.9%<br>Mort. rate sensit=13.2%<br>Mort. rate controls=6.8%<br>OR RvsS=5; 95%CI(1.2-20-4)<br>OR RvsNI=10.2;<br>95%CI(2.1-50) | Thailand | hospitaliz        | 14 resistant<br>38 sensitive<br>44 controls | age, ICU            | median(range)<br>resist=34(2-206)<br>sensitive=53.5(3-188)<br>controls=24.5(1-102) | patients were neonates in ICU                                       |

Table 2: Short extraction table of original articles on BSI mortality of CRAB infected patients vs CSAB infected patients

| Nr | Author                    | Study Period | Study type                         | Outcome  | Location    | Period of outcome | Population              | Matching criteria | LOS (days)   | Notes  |
|----|---------------------------|--------------|------------------------------------|--|-------------|-------------------|-------------------------|-------------------|--|--|
| 1  | Deris 2011 <sup>3</sup>   | no info      | Cross sectional case-control study | Mort. rate cases=64.3%<br>Mort. rate controls=40.5%<br>OR=0.38; 95%CI(0.11-1.36)<br>*Mort. rate cases=42.9%<br>*Mort. rate controls=24.3%<br>OR=2.33; 95%CI(0.64-8.65) | Malaysia    | hospitaliz        | 15 cases<br>41 controls | none              | median (IQR)<br>cases=32.3(16.4)<br>controls=32.8(25.0)              | *attributable mortality; within 72h from isolation |
| 2  | Esterly 2011 <sup>4</sup> | 01/05-12/08  | Retrospective cohort study         | Mort. rate cases=56.8%<br>Mort. rate controls=23.8%<br>Model1 OR=0.58; 95%CI(0.037-9.22)<br>Model2 OR=0.73;<br>95%CI(0.14-3.84)  | Chicago USA | hospitaliz        | 37 cases<br>42 controls | none              | Prior isolation<br>median (IQR)<br>cases=16(1-30)<br>controls=0(0-9) |  |

|   |                               |             |                                 |   |          |  |                          |          |   |  |
|---|-------------------------------|-------------|---------------------------------|---|----------|--|--------------------------|----------|---|--|
| 3 | Huang 2012 <sup>5</sup>       | 06/02-12/07 | Retrospective cohort study      | Mort. rate cases=35.5%<br>Mort. rate controls=20.7%<br>OR= 1.03 ; 95%CI(0.48-2.20)  | Taiwan   | 14 days                                  | 62 cases<br>164 controls | none     | Prior isolation<br>mean±SD<br>cases=35.9±33.6<br>controls=28.2±44   |  |
| 4 | Jamulitrat 2009 <sup>6</sup>  |             | Cohort study                    | Mort. rate cases=52.2%<br>Mort. rate controls=19.9%<br>aHR=1.7; 95%CI(0.9-2.9)  | Thailand | hospitaliz                               | 67 cases<br>131 controls | none     | median ±IQR<br>cases=37±32<br>controls=27±37                        |  |
| 5 | Kim 2012 <sup>7</sup>         | 06/07-06/10 | Retrospective study             | Mort. rate cases=49.1%<br>Mort. rate controls=9.5%<br>OR=7.29; 95%CI(1.57-33.8)   | Korea    | 14 days                                  | 53 cases<br>42 controls  | none     | Prior isolation<br>mean±SD<br>cases=30.0±33.3<br>controls=30.4±68.3 | the study differentiates those who received appropriate therapy from those who did not |
| 6 | Kumar 2014 <sup>8</sup>       | 01/10-12/12 | Retrospective chart review      | Mort. rate cases=27.3%<br>Mort. rate controls=9.4%  | India    | hospitaliz                               | 33 cases<br>32 controls  | age, ICU | no data   | patients were neonates in ICU  |
| 7 | Routsis 2010 <sup>9</sup>     | 09/04-01/06 | Prospective observational study | Mort. rate cases=43.3%<br>Mort. rate controls=46.9%   | Greece   | hospitaliz                               | 30 cases<br>66 controls  | none     | median (IQR)<br>cases=33(18.8-55.8)<br>controls=28.5(14.5-51.0)     |  |
| 8 | Tal-Jasper 2016 <sup>10</sup> | 01/07-12/12 | Retrospective cohort study      | a) Mort. rate cases=70.5%<br>Mort. rate controls=45.1%<br>b) Mort. rate cases=66.2%<br>Mort. rate controls=44.4%<br>c)Mort. rate cases=73.6%<br>Mort. rate controls=53.3%<br>OR 90days=0.6, 95%CI (0.1–2.3) | Israel   | a) hospitaliz<br>b)30 days<br>c) 90 days | 149 cases<br>91 controls | none     | median (IQR)<br>cases=21(10.8-39.5)<br>controls=10(7-20.5)          |  |

Table 3: Short extraction table of original articles on respiratory tract infection mortality of CRAB infected patients vs sensitive and vs non infected patients

| Nr | Author                              | Study Period | Study type              | Outcome  | Location | Period of outcome | Population                                  | Matching criteria | LOS (days)   | Notes                         |
|----|-------------------------------------|--------------|-------------------------|--|----------|-------------------|---|-------------------|--|-------------------------------|
| 1  | Thatrimontrichai 2016 <sup>11</sup> | 01/09-12/14  | Case-case-control study | Mort. rate resist=15.9%<br>Mort. sensit=7.7%<br>Mort. control=0% | Thailand | hospitaliz        | 63 resistant<br>13 sensitive<br>25 controls | age, ICU          | median(range)<br>resist=29(8-93)<br>sensitiv=20(8-31)<br>controls=22(8-68) | patients were neonates in ICU |

Table 4: Short extraction table of original articles on respiratory tract infection mortality of CRAB infected patients vs sensitive infected patients

| Nr | Author                              | Study Period | Study type                        | Outcome  | Location | Period of outcome | Population               | Matching criteria    | LOS (days)  | Notes   |
|----|-------------------------------------|--------------|-----------------------------------|--|----------|-------------------|--------------------------|----------------------|---|---|
| 1  | Chang 2011 <sup>12</sup>            | 01/05-12/07  | Retrospective observational study | Mort. rate cases=61.3%<br>Mort. rate controls=46.0%  | Taiwan   | hospitaliz        | 93 cases<br>87 controls  | none                 | after VAP onset<br>median±SD<br>cases=23.1±24.3<br>controls=26.7±24.3 | all patients were critically ill  |
| 2  | Garnacho-Montero 2003 <sup>13</sup> | 01/97-06/01  | Prospective cohort study          | Mort. rate cases=61.9%<br>Mort. rate controls=64.2%<br>*VAP related mortality<br>Mort. rate cases=38%<br>Mort. rate controls=35.7% | Spain    | hospitaliz        | 21 cases<br>14 controls  | underlying condition | mean±SD<br>cases=45.2±30.7<br>controls=53.9±50                        | cases treated with colistin, controls with imipenem-cilastatin<br>*occurring during treatment, when signs of pneumonia remained and due to septic shock |
| 3  | Zheng 2013 <sup>14</sup>            | 01/06-12/11  | Retrospective study               | Mort. rate cases=45.6%<br>Mort. rate controls=29.9%  | China    | 28 days           | 97 cases<br>145 controls | underlying condition | before pneu<br>mean±SD<br>cases=17.7±6.6<br>controls=18±6.2           |   |

Table 5 and Table 6 present the results of studies that include patients with different sites of infection. Almost all the articles specify the number of cases for the different infection sites but they do not report different mortalities based on the infection site. When it was possible the results are presented differentiating the mortality for each site of infection.

Table 5: Short extraction table of original articles on mortality of CRAB infected patients vs non infected patients for different infection sites

| Nr | Author                   | Study Period | Study type                 | Outcome  | Location | Period of outcome | Population                  | Matching criteria  | LOS (days)   | Notes  |
|----|--------------------------|--------------|----------------------------|--|----------|-------------------|-----------------------------|--|--|--|
| 1  | Henig 2015 <sup>15</sup> | 01/07-12/12  | Matched case-control study | Mort. rate cases=73%<br>Mort. rate controls=55%<br>aHR=2.33; 95%CI(2.08–2.6) | Israel   | hospitaliz        | 1190 cases<br>1190 controls | age, ward, season, Charlson score, LOS                             | matching criteria<br>median (range)<br>cases=18 (0–97)<br>controls=17 (0–96) | the study considers also 241 cases and controls with BSI but gives not info on their mortality |
| 2  | Nazer 2015 <sup>16</sup> | 01/10-12/13  | Matched case-control study | Mort. rate cases=73%<br>Mort. rate controls=61.2%                            | Jordan   | in ICU stay       | 142 cases<br>232 controls   | age, gender, APACHE II, type of malignancy, mechanical ventilation | median (IQR)<br>cases=12(6-13)<br>controls=3(1.7)                            | all patients were critically ill with cancer and in ICU  |

Table 6: Short extraction table of original articles on mortality of CRAB infected patients vs CSAB infected patients for different infection sites

| Nr | Author                       | Study Period | Study type                       | Outcome   | Location | Period of outcome | Population               | Matching criteria   | LOS (days)  | Notes                                   |
|----|------------------------------|--------------|----------------------------------|---|----------|-------------------|--------------------------|---------------------|---|---|
| 1  | Aydemir 2012 <sup>17</sup>   | 01/05-12/06  | Retrospective case-control study | Mort. rate cases=61.8%<br>Mort. rate controls=52.7%   | Turkey   | hospitaliz        | 110 cases<br>55 controls | none                | after isolation<br>mean±SD<br>cases=18.1±14.0<br>controls=15.7±12.3 |   |
| 2  | de Gouvea 2012 <sup>18</sup> | 01/02-01/09  | Retrospective study              | Mort. rate cases=44.4%<br>Mort. rate controls=29.0%<br>Inf. related. OR=0.73;<br>95%CI(0.12 – 4.47) | Brasil   | 30 days           | 18 cases<br>31 controls  | undelying condition | no data   | all patients had solid organ transplant |

|   |  |                     |   |  |                       |            |  |   |   |  |
|---|--|---------------------|---|--|-----------------------|------------|--|---|---|--|
|   |  |                     |   | Overall mort. OR=1,93;<br>95%CI(0.48 – 7.85)   |                       |            |  |   |   |  |
| 3 | del Mar<br>2005 <sup>19</sup>  | 10/01-<br>08/02     | Case-control<br>study                       | Mort. rate cases=43.3%<br>Mort. rate controls=19%<br>*Related mortality=30%  | Spain                 | 30 days    | 30 cases<br>31 controls                                  | same<br>period of<br>isolation  | attributable LOS=14<br>days   | cases were multi<br>resistant<br>* when infection<br>was established, by<br>clinical criteria, as<br>the primary cause<br>of death |
| 4 | Lautenbach<br>2009 <sup>20</sup>   | 01/89-<br>12/04     | Prospective<br>cohort study                 | Mort. rate cases=18%<br>Mort. rate<br>controls=21.2%<br>RR=0.85; 95% CI(0.52–<br>1.39)                             | New<br>Jersey,<br>USA | 30 days    | 89 cases<br>297<br>controls                              | none  | median(range)<br>cases=21(14-29)<br>controls=16(12-18)  |  |
| 5 | Lemos<br>2014 a <sup>21</sup>  | 04/06-<br>04/10     | Prospective,<br>multicentre<br>cohort study | Mort. rate cases=40%<br>Mort. rate<br>controls=12.2%<br>aHR=1.45; 95%CI(0.74-<br>2.87)                             | New<br>York,<br>USA   | 30 days    | 104 cases<br>61 controls                                 | ICU   | adjusted mean<br>cases=19.3<br>controls=16.2  | patients were in ICU   |
| 6 | Lemos<br>2014 b <sup>22</sup>  | up to<br>05/13      | Systematic<br>review and<br>meta-analysis   | crude OR=2.22; 95%<br>CI=1.66-2.98   | World                 |            |  |   |   |  |
| 7 | Sheng<br>2010 <sup>23</sup>  | 05/04-<br>11/06     | Multicentre<br>retrospective<br>study       | a) Mort. rate<br>cases=13.3%<br>Mort. rate controls=20%<br>b) Mort. rate cases=33%<br>Mort. rate<br>controls=17.5% | Taiwan                | hospitaliz | 30 cases<br>30 controls                                  | none  | Median (range)<br>a)cases=41 (5–282)<br>controls=29 (2–227)<br>b) cases=37 (1–218)<br>controls=23 (1–151) | a) colonized patients<br>b) infected patients  |
| 8 | The<br>Brooklyn<br>Antibiotic<br>Resistance<br>Task Force,<br>2002 <sup>24</sup> | 3<br>months<br>1999 | Matched case-<br>control study              | a) Mort. rate cases=34%<br>Mort. rate controls=27%<br>b) Mort. rate cases=20%<br>Mort. rate controls=30%           | USA                   | hospitaliz | a) 44 cases<br>33 controls<br>b) 10 cases<br>10 controls | age, site of<br>infect,<br>underlying<br>diseases,<br>operative<br>procedure,<br>type of<br>infection | after infection<br>median<br>cases=31.5<br>controls=13  | a) all cases and<br>controls<br>b) 10 matched pairs  |

Some of the detected studies reported pooled results for gram negative bacteria, or for *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. These were not included.

We detected different studies that reported treatment options for the resistant infections, comparing two or more therapeutic strategies. All these studies included mortality data of CRAB infected patients, but since they used just cases infected with CRAB and no control group, as defined by our eligibility criteria, these studies were not included in the results of this review.

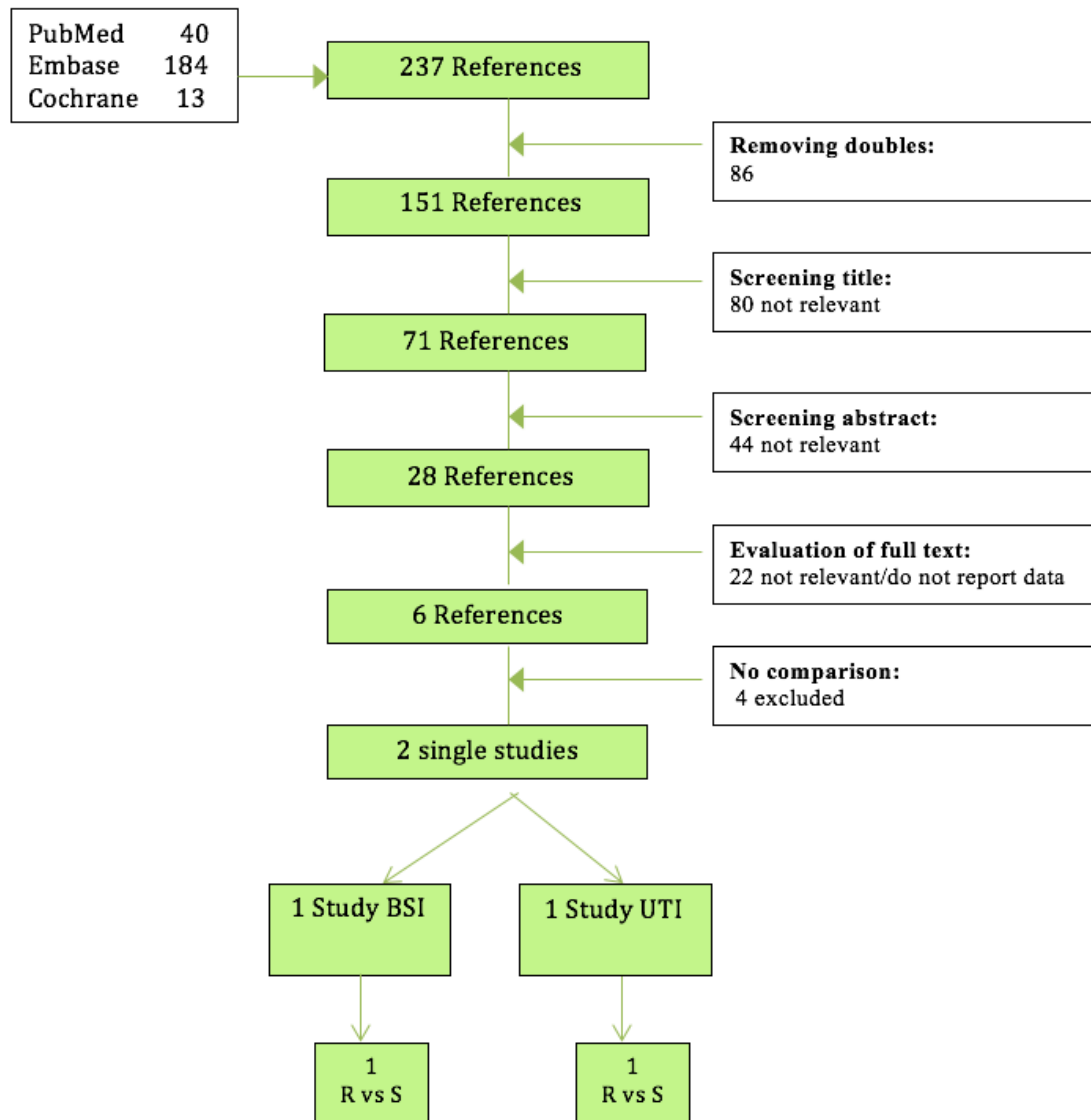
All studies were performed in healthcare settings and considered HAI, though some of them report cases of infection that originated in the community or that had the onset in the community, but none of them reported only CAI cases.

## 2. Colistin resistant *Acinetobacter baumannii*

To research the attributable case fatality and the attributable LOS to colistin resistant *Acinetobacter baumannii* (CoRAB) we performed 2 advanced searches on Pubmed using once the mesh term “*Acinetobacter baumannii*” AND all fields “colistin resistant”, and the second time the mesh term “*Acinetobacter baumannii*” AND all fields “colistin resistance”. Embase was searched for ‘*Acinetobacter baumannii*’ AND ‘colistin resistance’, and for ‘*Acinetobacter baumannii*’ AND ‘colistin resistant’. An advanced search on the Cochrane Library was performed using terms “*Acinetobacter baumannii*” AND “colistin”. No language restrictions were made, and no filters were applied.

The flow diagram, presented in Figure 2 describes the steps in the literature review of colistin resistant *Acinetobacter baumannii* infections. The results obtained using the two different key words in PubMed and Embase were aggregated.

Figure 2: Search for studies on colistin resistant *Acinetobacter baumannii*. Inclusion and exclusion diagram.



The following table 7 includes studies reporting mortality data for CoRAB. All information is reported as was presented in the original papers.

Table 7: Short extraction table of original articles on BSI mortality of CoRAN\* infected patients vs CoSAB infected patients

| Nr | Author                  | Study Period | Study type          | Outcome  | Location | Period of outcome        | Population               | LOS (days)  | Matching | Notes |
|----|-------------------------|--------------|---------------------|--|----------|--------------------------|--------------------------|---|----------|-------|
| 1  | Wang 2015 <sup>25</sup> | 1998-2008    | Retrospective study | a) Mort. rate cases=10.3%<br>Mort. rate controls=10.3%<br>b) Mort. rate cases=15.5%<br>Mort. rate controls=15% | Taiwan   | a) 14 days<br>b) 28 days | 58 cases<br>213 controls | prior infection<br>median (IQR)<br>cases=56 (32-101)<br>controls=37 (22-65) | none     |       |

\*The study in table 7 deals with *A. nosocomialis* instead of *A. baumannii* but we decided to include it in the review as eligible for the purposes of the project.

Table 8: Short extraction table of original articles on UTI mortality of CoRAB infected patients vs CoSAB infected patients

| Nr | Author                    | Study Period | Study type               | Outcome            | Location | Period of outcome | Population             | LOS (days) | Matching              | Notes   |
|----|---------------------------|--------------|--------------------------|--------------------|----------|-------------------|------------------------|------------|-----------------------|---|
| 1  | Taneja 2011 <sup>26</sup> | 02/07-06/08  | Prospective cohort study | Mort. rate both=0% | India    | hospitaliz        | 8 cases<br>42 controls | No data    | all bacteria were MDR | patients with complicated urinary tract infection |



We identified 4 additional studies<sup>27-30</sup> investigating the mortality due to CoRAB, but they did not use a comparison group. In these studies the mortality for the cases ranged from 0%-70%.

We did not apply any specific filter to the literature research because we wanted to be as broad as possible in including all the papers that had as subjects *Acinetobacter baumannii* and colistin resistance. The research produced numerous results, but not all of them were eligible for the purposes of this review.

Many detected papers reported studies on the efficacy of colistin on multi-drug resistant *Acinetobacter baumannii* strains, where multidrug resistance was defined as resistance to all antibiotics except for colistin.

The colistin resistant *Acinetobacter baumannii* infections are a relative new research topic, and it seems that no structured studies were conducted yet to investigate the burden of these infections in terms of attributable mortality or attributable length of stay in hospital.

### 3. Multidrug resistant *Acinetobacter baumannii*

For the purposes of this project a multidrug resistant isolate is defined as resistant to at least three classes of antimicrobial agents, all penicillins and cephalosporins (including inhibitor combinations), fluoroquinolones, and aminoglycosides. Here are excluded those resistant to carbapenem and/or to colistin. If an isolate is multidrug resistant and also resistant to carbapenem and/or colistin, it will be classified as resistant to the latter antibiotic.

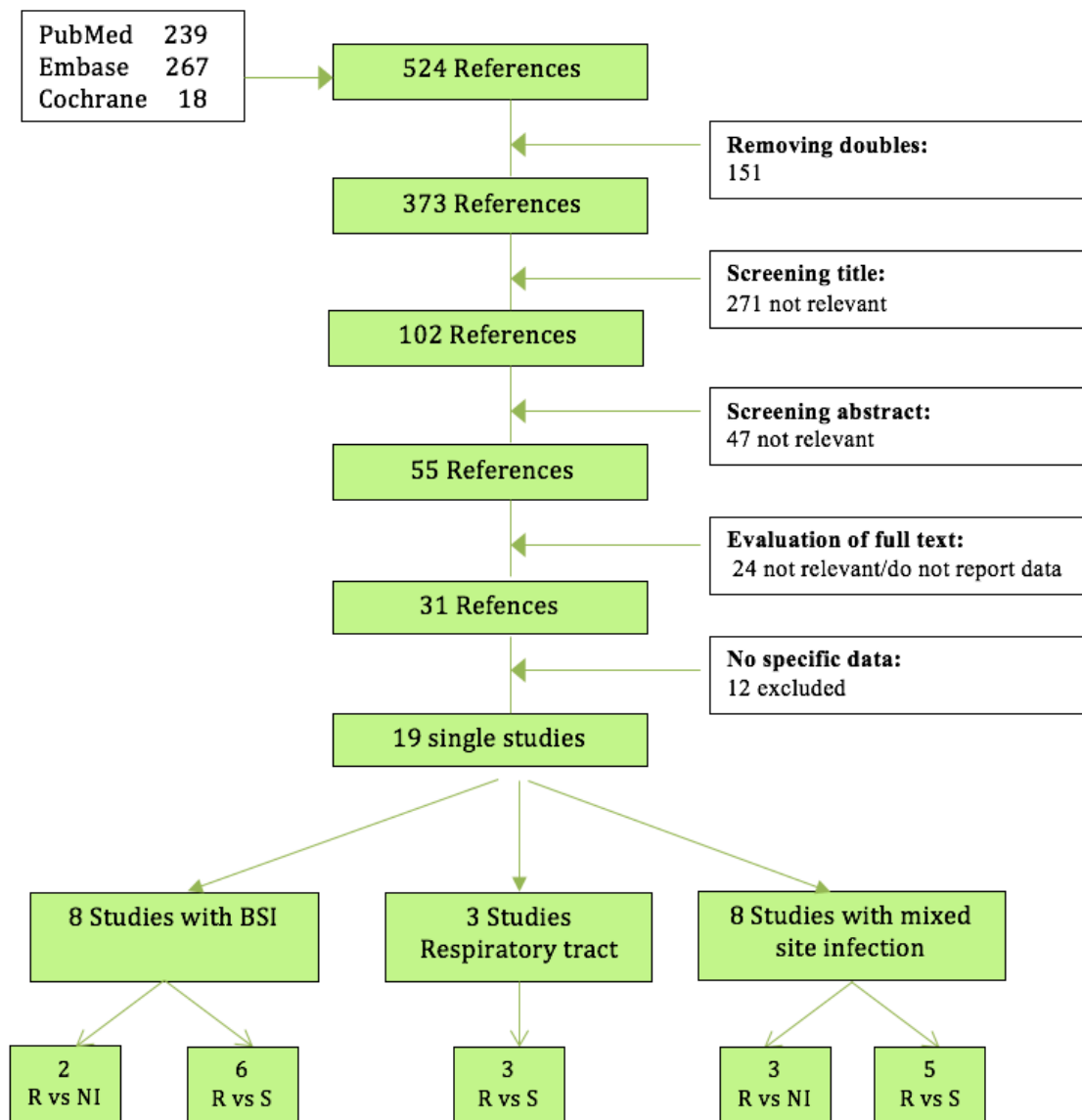
To research the attributable case fatality and the attributable LOS to multidrug resistant *Acinetobacter baumannii* (MDRAB) we performed 3 advanced searches on Pubmed using once the mesh term “*Acinetobacter baumannii*” AND all fields “multidrug resistant” AND all fields “mortality”, the second time the mesh term “*Acinetobacter baumannii*” AND all fields “multidrug resistance” AND all fields “mortality”, and the third time the mesh term “*Acinetobacter baumannii*” AND all fields “MDR” AND all fields “mortality”. All times a filter for human studies was applied. Embase was searched for ‘*Acinetobacter baumannii*’ AND ‘multidrug resistant’ AND ‘mortality’, and ‘*Acinetobacter baumannii* AND ‘multidrug resistance’ AND ‘mortality’. We applied a filter to include only human studies. Two advanced searches were also performed on the Cochrane Library, using once the terms “*Acinetobacter baumannii*” AND “multidrug resistant”, and the second time the terms “*Acinetobacter baumannii*” AND “multidrug resistance”. No language restrictions were made, and no further filters were applied.

The flow diagram, presented in Figure 3 describes the steps in the literature review of Multidrug resistant *Acinetobacter baumannii* infections. The results obtained using the different strings for PubMed, Embase and the Cochrane Library were aggregated.

Once identified the studies reporting relevant data, these were grouped based on the site of infection.

All eligible studies reported a MDRAB infected group and a control group. The latter could represent patients non infected (NI) or infected with susceptible (S) *A. baumannii* infections.

Figure 3: Search for studies on multidrug resistant *Acinetobacter baumannii*. Inclusion and exclusion diagram.



The following tables include studies reporting results for BSI, respiratory tract and for mixed site of infection due to MDRAB, based on the comparison group they used. All information is reported as was presented in the original articles.

Table 9: Short extraction table of original articles on BSI mortality of MDRAB infected patients vs non infected patients

| Nr | Author                         | Study Period | Study type                     | Outcome   | Location  | Period of outcome                         | Population               | Matching criteria | LOS (days)   | Notes  |
|----|--------------------------------|--------------|--------------------------------|---|-----------|---|--------------------------|-------------------|--|--|
| 1  | Al Jarousha 2009 <sup>31</sup> | 02/04-01/05  | Prospective case-control study | Mort. cases=37.5%<br>Mort. controls=12%   | Palestine | hospitaliz                                | 40 cases<br>100 controls | age, birth weight | no specific data   | patients were in neonatal ICU                |
| 2  | Gulen 2015 <sup>32</sup>       | 01/07-12/10  | Retrospective cohort study     | a) Mort. cases=30%<br>b) Mort. cases=52.4%<br>c) Mort. Cases=53.7%<br>Attribut. mort.=24.4% | Turkey    | a) 14 days<br>b) 28 days<br>c) hospitaliz | 41 cases<br>45 controls* | BSI               | before BSI<br>mean±SD<br>cases=25.49±21.47<br>controls=22.80±19.28 | *patients had other gram-negative infections |

Table 10: Short extraction table of original articles on BSI mortality of MDRAB infected patients vs MDSAB infected patients

| Nr | Author                         | Study Period | Study type                         | Outcome  | Location     | Period of outcome        | Population              | Matching criteria                | LOS (days)   | Notes   |
|----|--------------------------------|--------------|------------------------------------|--|--------------|--------------------------|-------------------------|----------------------------------|--|---|
| 1  | Anunnatsiri 2011 <sup>33</sup> | 01/05-12/07  | Retrospective study                | Mort. cases=91.7%<br>Mort. controls=48%<br>OR=11.92;<br>95%CI(2.30-61.83)          | Thailand     | hospitaliz               | 24 cases<br>25 controls | none                             | before BSI<br>median (range)<br>cases=21.5(4-161)<br>controls=14(2-86) |   |
| 2  | Fitzpatrick 2015 <sup>34</sup> | 06/05-10/12  | Retrospective cohort study         | a) Mort. cases=36%<br>Mort. controls=8%<br>b) Mort. cases=44%<br>Mort. controls=8% | Chicago, USA | a) 14 days<br>b) 30 days | 92 cases<br>24 controls | none                             | Post culture<br>median(range)<br>cases=11.5(2-69)<br>controls=6(2-38)  |   |
| 3  | Guo 2016 <sup>35</sup>         | 06/12-06/15  | Retrospective study                | Mort. cases=44.8%<br>Mort. controls=4.3%<br>OR=26.3; 95%CI(3.0-231.4)              | China        | 30 days                  | 64 cases<br>23 controls | none                             | in ICU<br>mean<br>cases=51<br>controls=5                               |   |
| 4  | Lee 2007 <sup>36</sup>         | 04/96-08/01  | Retrospective matched cohort study | a) Mort. cases=47.8%<br>Mort. controls=39.1%<br>b) Mort. cases=34.8%               | Taiwan       | hospitaliz               | 46 cases<br>46 controls | sex, age, severity of underlying | mean±SD<br>cases=54.2±42.8<br>controls=34.1±30.5                       | a) crude mortality<br>b) sepsis related mortality |

|   |                             |             |                     |   |        |            |                           |                   |  |  |
|---|-----------------------------|-------------|---------------------|---|--------|------------|---------------------------|-------------------|--|--|
|   |                             |             |                     | Mort. controls=13.0%  |        |            |                           | and acute illness |  |  |
| 5 | Lee 2010 <sup>37</sup>      | 01/00-12/05 | Retrospective study | Mort. cases=32%<br>Mort. controls=8,3%<br>OR=7.46;<br>95%CI(3.78-14.70) | Taiwan | 30 days    | 147 cases<br>144 controls | none              | no specific data                               | the study investigated the difference between gen. sp.2 vs gen. sp. 3 data were extrapolated |
| 6 | Smolyako 2003 <sup>38</sup> | 01/05-12/05 | Prospective study   | Mort. cases=29.4%<br>Mort. controls=11.6%<br>OR=4                       | Israel | hospitaliz | 51 cases<br>43 controls   | none              | mean±SD<br>cases=37.7±30<br>controls=24.3±18.3 |  |

Table 11: Short extraction table of original articles on respiratory tract infection mortality of MDRAB infected patients vs MDSAB infected patients

| Nr | Author                    | Study Period | Study type                 | Outcome  | Location | Period of outcome           | Population               | Matching criteria | LOS (days)   | Notes                                 |
|----|---------------------------|--------------|----------------------------|--|----------|-----------------------------|--------------------------|-------------------|--|---------------------------------------|
| 1  | Cai 2012 <sup>39</sup>    | 01/09-08/11  | Prospective study          | Mort. cases=18.26%<br>Mort. controls=4.44%   | China    | hospitaliz                  | 115 cases<br>45 controls | ward              | in ICU<br>mean±SD<br>cases=17.39±7.05<br>controls=14.43±3.92 | patients were children with pneumonia |
| 2  | Inchai 2015 <sup>40</sup> | 01/05-12/11  | Retrospective cohort study | a)Mort. cases=31.9%<br>Mort. controls=21.2%<br>b)Mort. cases=44.4%<br>Mort. controls=27.3%<br>HR=1.03;<br>95%CI(0.44–2.45) | Thailand | a) 30 days<br>b) hospitaliz | 72 cases<br>33 controls  | ICU               | no data  | patients were in ICU                  |
| 3  | Park 2006 <sup>41</sup>   | 01/02-11/04  | Retrospective study        | Mort. cases=58.8%<br>Mort. controls=40%  | Korea    | hospitaliz                  | 17 cases<br>30 controls  | no data           | mean±SD<br>cases=42.8±24.0<br>controls=66.2±56.1             |                                       |

Table 12 and Table 13 present results of studies that include patients with different sites of infection. Almost all the articles specify the number of cases for the different infection sites but they do not report different mortalities based on the infection site. When it was possible the results are presented differentiating the mortality for each site of infection.

Table 12: Short extraction table of original articles on mortality of MDRAB infected patients vs non infected patients for different infection sites

| Nr | Author                    | Study Period | Study type                                    | Outcome  | Location        | Period of outcome | Population                | Matching criteria                       | LOS (days)                                       | Notes   |
|----|---------------------------|--------------|---|--|-----------------|-------------------|---------------------------|---|--|---|
| 1  | Abbo 2007 <sup>42</sup>   | 01/01-06/01  | Retrospective matched cohort study            | Mort. cases=36%<br>Mort. controls=21%<br>OR=2.21, 95%CI(1.17-4.16)   | Israel          | hospitaliz        | 118 cases<br>118 controls | ward, month of hosp, LOS before culture | median cases=17<br>controls=11                   |   |
| 2  | Fukuta 2013 <sup>43</sup> | 01/08-12/11  | Case-control study                            | Mort. cases=41.9%<br>Mort. controls=29%                              | Pittsburgh, USA | 90 days           | 31 cases<br>62 controls   | underlying condition                    | median(IQR) cases=28 (9-59)<br>controls=10(5-18) | patients had cancer                                 |
| 3  | Lee 2016 <sup>44</sup>    | 01/12-12/14  | Retrospective propensity-matched cohort study | Mort. cases=32%<br>Mort. controls=36.8%<br>OR=3.64; 95%CI(1.80-7.37) | Korea           | hospitaliz        | 122 cases<br>122 controls | propensity score                        | mean±SD cases=40.3±40.6<br>controls=24.6±28      | presence of MDRAB isolate without signs or symptoms |

Table 13: Short extraction table of original articles on mortality of MDRAB infected patients vs MDSAB infected patients for different infection sites

| Nr | Author                     | Study Period | Study type                                    | Outcome   | Location       | Period of outcome | Population  | Matching criteria | LOS (days)   | Notes   |
|----|----------------------------|--------------|---|---|----------------|-------------------|---|-------------------|--|---|
| 1  | Brahmi 2007 <sup>45</sup>  | 01/04-12/05  | Prospective study                             | Mort. cases=67.5%<br>Mort. controls=46.7%   | Tunisia        | hospitaliz        | 29 cases<br>34 controls                                   | ward              | in ICU<br>mean±SD cases=27±17.8<br>controls=32.3±23.9  | patients were in ICU  |
| 2  | Daniels 2008 <sup>46</sup> | 06/03-06/06  | Retrospective propensity-matched cohort study | a)Mort. cases=15.8%<br>Mort. controls=9.5%<br>b) Mort. cases=14.3%<br>Mort. controls=9.5% | Tennessee, USA | 28 days           | a)146 cases<br>42 controls)<br>b) 42 cases<br>42 controls | propensity score  | median (IQR) cases=32.5(22-51)<br>controls=26.5(16-43) | patients were in ICU<br>a) all patients<br>b) matched pairs |

|   |                               |             |  |  |          |            |                            |                      |   |                                    |
|---|-------------------------------|-------------|--|--|----------|------------|----------------------------|----------------------|---|------------------------------------|
| 3 | Lemos 2011 <sup>47</sup>      | 04/06-04/10 | Prospective, observational multicentre study | a) Mort. cases=31%<br>Mort. controls=9%<br>b) Mort. cases=41%<br>Mort. controls=9%<br>b) RR=1,219;<br>95%CI(0,923–1,611) | Colombia | 14 days    | 103 cases<br>62 controls   | ICU                  | median(IQR)<br>pre ICU<br>cases=4(1.2-18)<br>controls=5(1.5-22.3)<br>in ICU<br>cases=15(13-60)<br>controls=13(8-44) | patients were in ICU               |
| 4 | Pierri 2015 <sup>48</sup>     | 01/09-12/11 | Retrospective matched cohort study           | Mort. cases=57%<br>Mort. controls=46%  | Italy    | hospitaliz | 14 cases<br>26 controls    | propensity score     | mean±SD<br>cases=36±20<br>controls=25±18  | patients underwent cardiac surgery |
| 5 | Zilberberg 2016 <sup>49</sup> | 01/09-12/13 | Retrospective cohort study                   | Mort. cases=23.7%<br>Mort. controls=12.7%  | USA      | hospitaliz | 1171 cases<br>252 controls | underlying condition | no data   | patients had pneumonia or sepsis   |

The vast majority of papers containing information on mortality did not report a comparison group.

Many studies reported treatment options for the resistant infections, but since they used just cases infected with MRDAB and no control group, as defined by our eligibility criteria, these studies were not included.

All studies were performed in healthcare settings though some of them report cases of infection that originated in the community, but none of them treated only patients with infection onset in the community.

The studies that included patients with MDRAB which were also resistant to carbapenems were also not included.

We did not perform a literature review for third-generation cephalosporin resistant *Acinetobacter baumannii* (3GCRAB), but we decided to report here the results of a multicentre European study<sup>50</sup> that investigated the mortality of patients infected with 3GCRAB. The authors compared patients with resistant and susceptible *A. baumannii* to cefetizime (3GCRAB vs 3GCSAB), for BSI and respiratory tract infections. Table 14 reports the characteristics and results of this study.

Table 14: Short extraction table of the original article on mortality of 3GCRAB infected patients vs 3GCSAB infected patients for BSI and respiratory tract infections

| Nr | Author                     | Study Period | Study type               | Outcome  | Location | Period of outcome   | Population  | Matching criteria | LOS (days)  | Notes  |
|----|----------------------------|--------------|--------------------------|--|----------|---------------------|---|-------------------|---|--|
| 1  | Lambert 2011 <sup>50</sup> | 01/05-12/08  | Prospective cohort study | a) Mort. cases=43%<br>Mort. controls=55%<br>aHR=0.8; 95%CI(0.3-2.1)<br>b) Mort. cases=38%<br>Mort. controls=40%<br>aHR=1.0; 95%CI(0.6-1.8) | Europe   | ICU hospitalization | a)31 cases<br>11 controls<br>b)130 cases<br>43 controls | ICU               | From infection to discharge median (IQR)<br>a)cases= 20 (7–38)<br>controls=9 (2-13)<br>b)cases= 14 (11–26)<br>controls= 25(14-40) | patients were in ICU<br>a)patients with BSI<br>b)patients with pneumonia |

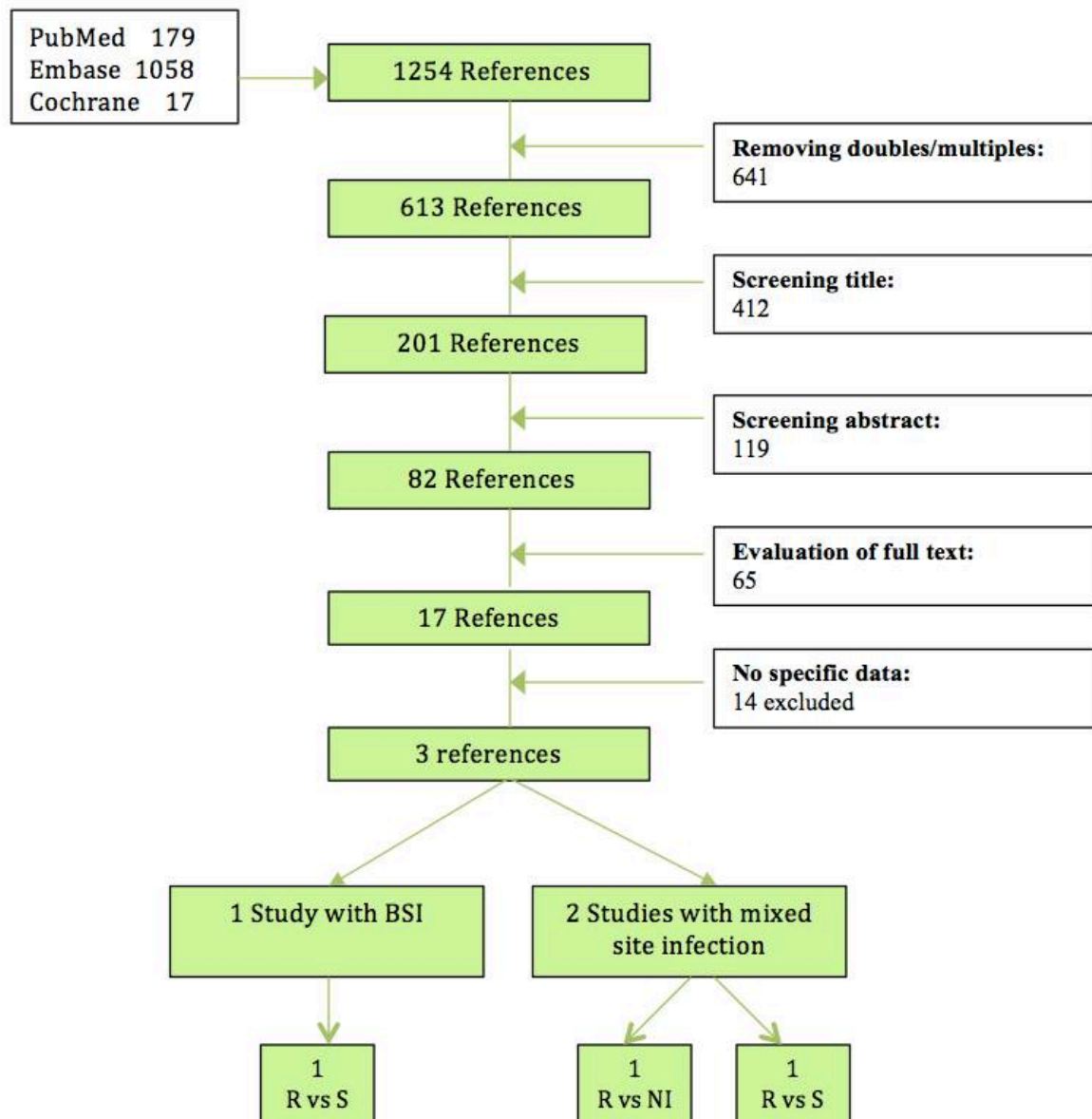
#### 4. Carbapenem resistant *Escherichia coli*

To research the attributable case fatality and the attributable LOS to carbapenem resistant *Escherichia coli* (CREC) we performed an advanced search on Pubmed using “*Escherichia coli*” [MeSH Terms] AND “carbapenem resistance” all fields, together with the string “*Escherichia coli*” [MeSH Terms] AND “carbapenem resistant” all fields. No filters were applied. Embase was searched for ‘*Escherichia coli*’ AND ‘carbapenem resistance’, and for ‘*Escherichia coli*’ AND ‘carbapenem resistant’. No filters were applied. An advanced search on the Cochrane Library was performed using terms “*Escherichia coli*” AND “carbapenem”. Studies on animals, cells and tissues, as well as case report studies were excluded from the results. No language restrictions were made to any database.

The following flow diagram describes the steps in the literature review of carbapenem resistant *Escherichia coli* infections.



Figure 4: Search for studies on carbapenem resistant *Escherichia coli*. Inclusion and exclusion diagram.



The following tables include studies reporting results for BSI and mixed site infection, based on the comparison group they used, carbapenem susceptible *Escherichia coli* (CSEC) infected patients or non-infected (NI). All information is reported as was presented in the original papers

Table 15: Short extraction table of original articles on BSI mortality of CREC infected patients vs CSEC infected patients

| Nr | Author                   | Study Period | Study type                 | Outcome  | Location | Period of outcome                            | Population              | Matching criteria                                       | LOS (days)   | Notes                                       |
|----|--------------------------|--------------|----------------------------|--|----------|--|-------------------------|---|--|---|
| 1  | Chang 2011 <sup>51</sup> | 01/06-12/08  | Matched case-control study | a)Mort. rate cases=47.06%<br>Mort. rate controls=38.24%<br>b)Mort. rate cases=70.59%<br>Mort. rate controls=47.06%<br>c)Mort. rate cases=94.12%<br>Mort. rate controls=50% | Taiwan   | a) ≤14 days<br>b) ≤ 28 days<br>c) hospitaliz | 17 cases<br>34 controls | gender, age, year of hosp, length stay before isolation | mean±SD (min-max)<br>cases=68.4±56.4 (7-161)<br>controls=35.8±34.5 (4-141) | Cases are non-susceptible, MIC non reported |

Table 16 and Table 17 present the results of studies that include patients with different sites of infection. Almost all the articles specify the number of cases for the different infection sites but they do not report different mortalities based on the infection site.

Table 16: Short extraction table of original articles on mortality of CREC infected patients vs non infected patients for different infection sites

| Nr | Author                     | Study Period | Study type         | Outcome   | Location      | Period of outcome | Population             | LOS (days)   | Matching                    | Notes   |
|----|----------------------------|--------------|--------------------|---|---------------|-------------------|------------------------|--|-----------------------------|---|
| 1  | Epstein 2014 <sup>52</sup> | 01/13-12/13  | Case-control study | Mort. rate cases=25%*<br>Mort. rate controls=0% | Illinois, USA | hospitaliz        | 8 cases<br>27 controls | median cases=8.5<br>controls=25.0<br>mean(SD)[range]<br>cases=13.3 (12.0) [1-37] | patients from the same ward | patients from the same ward<br>* death not related to |

|  |  |  |  |  |  |  |  |  |                                 |  |      |
|--|--|--|--|--|--|--|--|--|---------------------------------|--|------|
|  |  |  |  |  |  |  |  |  | controls=30.2 (13.2)<br>[14-65] |  | CREC |
|--|--|--|--|--|--|--|--|--|---------------------------------|--|------|

\* deaths not related to CREC (author's statement)

Table 17: Short extraction table of original articles on mortality of CREC infected patients vs CSEC infected patients for different infection sites

| Nr | Author                 | Study Period  | Study type                  | Outcome   | Location | Period of outcome | Population               | Matching          | LOS (days)                                       | Notes |
|----|------------------------|---------------|-----------------------------|---|----------|-------------------|--------------------------|-------------------|--|-------|
| 1  | Ahn 2014 <sup>53</sup> | 10/06 - 12/10 | Matched case-controls study | Mort. rate cases=14.8%<br>Mort. rate controls=10.2% | Korea    | 28 days           | 57 cases<br>114 controls | Site of infection | mean±SD<br>cases=26.6±37.9<br>controls=13.1±41.3 |       |

Table 18: Short extraction table of original articles on mortality of CREC infected patients without a control group

| Nr | Study                     | Study Period | Study type                              | Outcome                | Location       | Period of outcome | Population | Matchin g | LOS (days) | Notes                                  |
|----|---------------------------|--------------|---|------------------------|----------------|-------------------|------------|-----------|------------|--|
| 1  | Balkan 2014 <sup>54</sup> | 02/11-03/13  | Retrospective nested case-control study | Mort. rate cases=50%   | Turkey         | hospitaliz        | 8 cases    | none      | No data    | comp. with klebsiella and enteorbacter |
| 2  | Poirel 2014 <sup>55</sup> | 03/12-09/12  | Observational study                     | Mort. rate cases=33.3% | Bulgaria       | hospitaliz        | 12 cases   | none      | No data    | study on Enterobacteriaceae            |
| 3  | Porwal 2014 <sup>56</sup> | 05/11-05/12  | Retrospective study                     | Mort. rate cases=38.5% | Chennai, India | 30 days           | 13 cases   | none      | No data    | study on Gram-                         |
| 4  | Shukla 2013 <sup>57</sup> |              | Retrospective study                     | Mort. rate cases= 6%   | Mumbai, India  | hospitaliz        | 17 cases   | none      | No data    | study on Gram-                         |

The studies included in table 18 are not eligible studies since they do not have a control group. They are part of this report as further possible source of information on the mortality of carbapenem resistant *Escherichia coli* infections, since the number of eligible studies detected with this literature review was limited. These studies included investigated the mortality of Gram negative or Enterobacteriaceae, only comparing the different bacteria on each group.

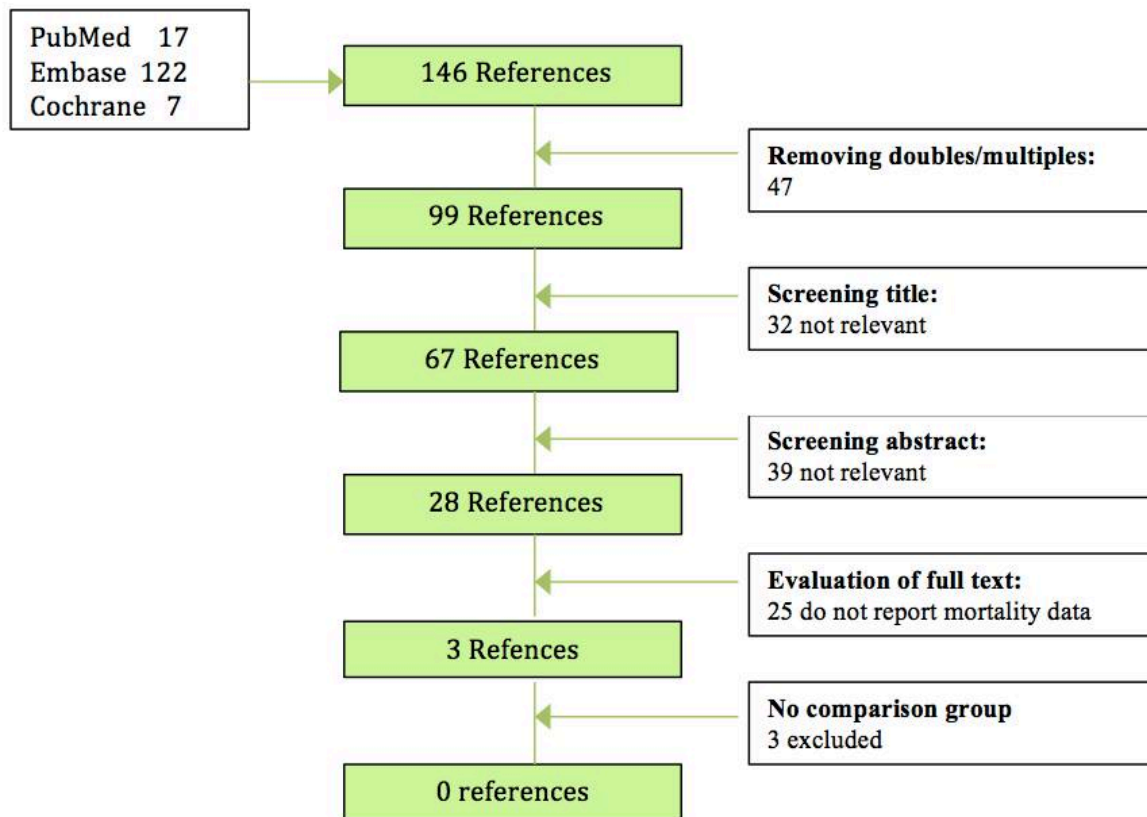
## 5. Colistin resistant *Escherichia coli*

*Escherichia coli* resistance to colistin was attributed to chromosomal mutations until November 2015, when Liu et al.<sup>58</sup> published a research, from China, showing that the resistance, in animals and humans, was due to the mcr-1 gene, which can be horizontally transmitted through plasmids. After the publication the gene was detected in other countries, both in animals and humans.

To research the attributable case fatality and the attributable LOS to colistin resistant *Escherichia coli* (CoREC) we performed 2 advanced searches on Pubmed using once the mesh term “*Escherichia coli*” AND all fields “colistin resistant”, and the second time the mesh term “*Escherichia coli*” AND all fields “colistin resistance”. Embase was searched for ‘*Escherichia coli*’ AND ‘colistin resistance’, and for ‘*Escherichia coli*’ AND ‘colistin resistant’. An advanced search on the Cochrane Library was performed using terms “*Escherichia coli*” AND “colistin”. No language restrictions were made, and no filters were applied.

The flow diagram, presented in Figure 5 describes the steps in the literature review of colistin resistant *Escherichia coli* infections. The results obtained using the two different key words in PubMed and Embase were aggregated.

Figure 5: Search for studies on colistin resistant *Escherichia coli*. Inclusion and exclusion diagram.



The following table includes 3 studies reporting mortality data for CoREC infected patients without a comparison group. Though these studies do not fulfil our eligibility criteria, they were reported since no other evidence on the mortality due CoREC was available. All information is reported as was presented in the original papers.

Table 19: Short extraction table of original articles on CoREC infected patients

| Nr | Author                        | Study Period | Infection site | Study type                 | Outcome       | Location             | Period of outcome | Population | Matching criteria | LOS (days)                                | Notes  |
|----|-------------------------------|--------------|----------------|----------------------------|---------------|----------------------|-------------------|------------|-------------------|---|--|
| 1  | Kontopidou 2011 <sup>28</sup> | 11/03-12/06  | not defined    | Retrospective cohort study | Mort. rate=0% | Athens, Greece       | hospitaliz        | 2 cases    | none              | no data                                   | the study analysed Gram- bacteria                                  |
| 2  | Nordmann 2016 <sup>59</sup>   | 2015         | BSI            | Prospective cohort study   | Mort. rate=0% | Switzerland          | hospitaliz        | 2 cases    | none              | no data                                   | the first 2 cases in a row in the hosp                             |
| 3  | Oostdijk 2011 <sup>60</sup>   | 01/08-10/10  | different      | Retrospective cohort study | no data       | Utrecht, Netherlands | hospitaliz        | 11 cases   | none              | *median(range, IQR) cases=29 (8-96, 29.8) | *info based on 18 patients (not just the EC cases) with Gram- inf. |

We did not apply any filter to the literature research because we wanted to be as broad as possible in including all the papers that had *Escherichia coli* and colistin resistance as subjects. The first search yielded numerous studies; however, after analysing them the vast majority was excluded because not relevant for our study question and none of them fulfilled our eligibility criteria.

Many papers reported CoREC strains in animal samples or referred to molecular characterization of resistant bacteria. Resistance in humans was analysed in studies which included different Gram negative bacteria or all Enterobacteriaceae. When it was possible, the results of mortality due to CoREC infections were extrapolated from these studies, otherwise they were excluded as unspecific for our research purpose.

The colistin resistant *Escherichia coli* infections are a relative new research topic, and it seems that no structured study was yet conducted to investigate the burden of these infections in terms of attributable mortality or attributable length of stay in hospital

## 6. Third-generation Cephalosporin resistant *Escherichia coli*

The resistance to the 3<sup>rd</sup> generation of cephalosporin is due to the production of extended-spectrum beta-lactamase enzymes (ESBL). These enzymes can deactivate extended spectrum (3<sup>rd</sup> generation) cephalosporins (e.g., ceftazidime, cefotaxime, and ceftriaxone) and monobactams (e.g., aztreonam).

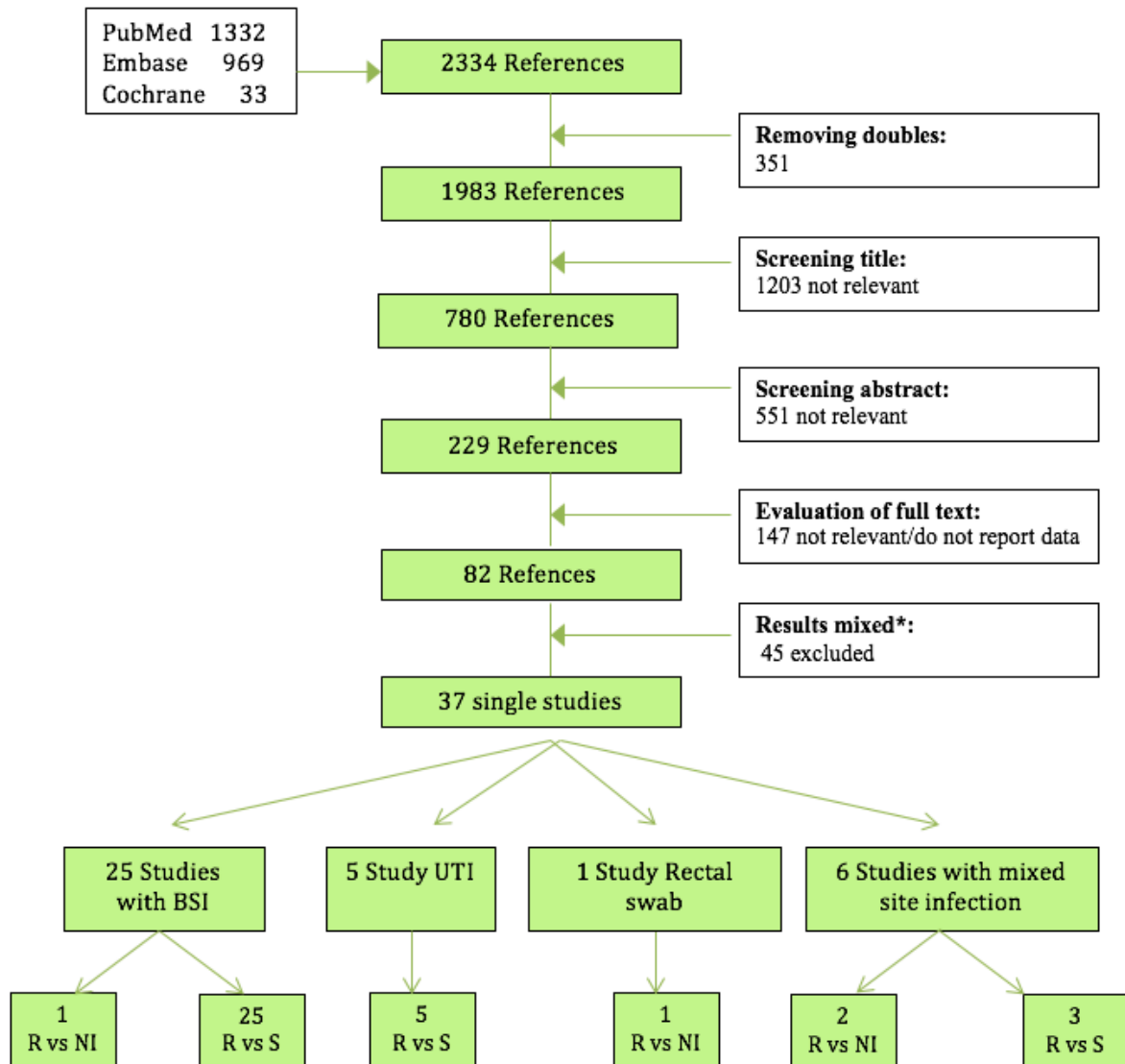
The guidelines internationally accepted for the detection of ESBL-producing bacteria, including *Escherichia coli*, have been defined in 1999 by the US-based National Committee for Clinical Laboratory Standards (now the Clinical and Laboratory Standards Institute). For the purpose of these review, 3<sup>rd</sup> generation cephalosporin resistant *Escherichia coli* (3GCREC) and ESBL producing *Escherichia coli* (ESBL-EC) will be considered equivalent.

To research the attributable case fatality and the attributable LOS to third-generation cephalosporin resistant *Escherichia coli* (3GCREC) we performed 2 advanced searches on Pubmed using once the mesh term “*Escherichia coli*” AND all fields “third generation cephalosporin”, and the second time the mesh term “*Escherichia*” AND all fields “ESBL OR extended-spectrum beta lactamase”. Both times a filter for human studies was applied. Embase was searched for ‘*Escherichia* AND third generation cephalosporin’, and ‘*Escherichia coli* AND (ESBL OR extended-spectrum beta-lactamase)’. We applied a filter to include only human studies and to exclude abstracts that did not have a correspondent article. An advanced search on the Cochrane Library was performed using terms “*Escherichia coli*” AND “third generation cephalosporin”, plus a second search using “*Escherichia coli*” AND “ESBL OR extended-spectrum beta-lactamase”. No language restrictions were made, and filter for research in humans was applied.

The flow diagram, presented in Figure 6 describes the steps in the literature review of 3<sup>rd</sup> generation cephalosporin resistant *Escherichia coli* infections. The results obtained using ESBL and 3<sup>rd</sup> generation cephalosporin as key words were aggregated.

Once identified the studies reporting relevant data, these were grouped based on the site of infection. The majority of them reported BSI infections, even though not all of them had a control group.

Figure 6: Search for studies on 3<sup>rd</sup> generation cephalosporin resistant *Escherichia coli*. Inclusion and exclusion diagram.



\*These studies reported results for ESBL-*Enterobacteriaceae* or together for *E.coli* and *Klebsiella pneumoniae*.

The following tables include studies reporting results for BSI, UTI, rectal swab and for mixed site of infection due to 3GCREC, based on the comparison group they used. All information is reported as was presented in the original papers.



Table 20: Short extraction table of original articles on BSI mortality of 3GCREC infected patients vs 3GCSEC infected patients and vs non infected patients

| Nr | Author                       | Study Period | Study type                                 | Outcome   | Location        | Period of outcome          | Population  | Matching criteria    | LOS (days)  | Notes |
|----|------------------------------|--------------|--|---|-----------------|----------------------------|---|----------------------|---|-------|
| 1  | de Kraker 2011 <sup>61</sup> | 07/07-06/08  | Prospective parallel matched double cohort | <p>a)C1: Mort. resist=32%<br/>Mort. control=6%<br/>OR=4.6, 95%CI(1.7–12.3)<br/>C2: Mort. sensit=17%<br/>Mort. control=7%<br/>OR=1.9; 95%CI(1.4–2.5)<br/>OR R vs S= 2.5; 95%CI(0.9–6.8)</p> <p>b)C1: Mort. resist=36%<br/>Mort. control=5%<br/>HR=5.7; 95%CI(2.5–13.0)<br/>C2:Mort. sensit=17%<br/>Mort. control=7%<br/>HR=2.0; 95%CI(1.5–2.5)<br/>HR R vs S=2.9; 95%CI(1.2–6.9)</p> | 13 EU countries | a)30 days<br>b) hospitaliz | C1) 111 resistant<br>204 NI controls for resistant<br>C2) 1110 sensitive<br>2084 controls for sensitive | LOS before enrolment | median (IQR)<br>resist=12(6-25)<br>sensit=10(6-17)<br>control=6(3-16) |       |

Table 21: Short extraction table of original articles on BSI mortality of 3GCREC infected patients vs 3GCSEC infected patients

| Nr | Author                               | Study Period | Study type                       | Outcome  | Location | Period of outcome     | Matching  | Population                 | LOS (days)   | Notes   |
|----|--------------------------------------|--------------|----------------------------------|--|----------|-----------------------|---|----------------------------|--|---|
| 1  | Anunnatsiri 2012 <sup>62</sup>       | 2005-2006    | Retrospective case-control study | Mort. cases=29%<br>Mort. controls= 11.5%   | Thailand | hospitaliz            | none  | 32 cases<br>113 controls   | prior BSI<br>median (range)<br>cases=4 (0-66)<br>controls=0 (0-82) |   |
| 2  | Apisarntharak 2008 <sup>63</sup>     | 07/03-12/07  | Retrospective case-control study | Mort. cases=8%<br>Mort. controls= 15%*   | Thailand | hospitaliz            | microorganism, site of infection, unit, date of admission | 24 cases<br>108 controls * | median (range)<br>cases=8 (1-43)<br>controls=6 (3-15)              | *controls have EC or KP   |
| 3  | Cornejo-Juarez 2012 <sup>64</sup>    | 2004-2009    | Retrospective case-control study | a)Mort. cases=38.6%<br>Mort. controls= 21.6%<br>b)Mort. cases=19.3%<br>Mort. controls= 36.4% | Mexico   | 60 days               | unit  | 88 cases<br>88 controls    | difficult to interpret   | patients with haematological malignancies<br>a) death related to infection<br>b) death not related to infection |
| 4  | Courpon-Claudinon 2011 <sup>65</sup> | 2005         | Prospective multi-centre study   | Mort. cases=30.8%<br>Mort. controls= 12.3%   | France   | hospitaliz            | none  | 39 cases<br>1012 controls  | no data  | surveillance study  |
| 5  | Ortega 2009 <sup>66</sup>            | 01/91-12/07  | Prospective study                | Mort. cases=15.6%<br>Mort. controls= 7.6%  | Spain    | a) 7days<br>b) 30days | none  | 211 cases<br>3247 controls | no data  |   |
| 6  | Trecarichi 2009 <sup>67</sup>        | 01/00-12/07  | Retrospective cohort             | Mort. cases=42.3%<br>Mort. controls= 5.6%<br>OR=8.84; 95%CI(1.48-52.91)                      | Italy    | 30 days               | none  | 26 cases<br>36 controls    | no data  | patients with haematological malignancies   |

|    |                                   |             |  |   |                   |                                     |   |                          |   |   |
|----|-----------------------------------|-------------|--|---|-------------------|-------------------------------------|---|--------------------------|---|---|
| 7  | Hsieh 2010 <sup>68</sup>          | 01/05-12/06 | Retrospective cohort                       | Mort. cases=21.1%<br>Mort. controls= 12.2%  | Taiwan, China     | 30 days                             | emergency room patients                           | 19 cases<br>385 controls | mean ( $\pm$ SD)<br>cases=15.5( $\pm$ 8.5)<br>controls=6.1( $\pm$ 6.9)  | patients with community onset infection   |
| 8  | Tumbarello 2010 <sup>69</sup>     | 01/06-12/06 | Retrospective cohort                       | Mort. cases=29.7%<br>Mort. controls= 6.1%<br>OR=4.43; 95%CI(2.46-7.95)                      | Italy             | 21 days                             | none  | 37 cases<br>97 controls  | mean ( $\pm$ SD)<br>cases=20( $\pm$ 17)<br>controls=13( $\pm$ 9)        |   |
| 9  | Gudiol 2010 <sup>70</sup>         | 01/06-10/08 | Prospective cohort                         | a)Mort. cases=12%<br>Mort. controls= 8%<br>b)Mort. cases=35%<br>Mort. controls= 19%         | Spain             | a) 7days<br>b) 30days               | underlying condition                              | 17 cases<br>118 controls | no data   | patients with cancer/stem cell transplant |
| 10 | Ho 2002 <sup>71</sup>             | 01/97-12/98 | Retrospective case-control study           | Mort. cases=18%<br>Mort. controls= 7%   | China             | 30 days                             | specialty, sex, age( $\pm$ 10), date of isolation | 50 cases<br>100 controls | no data   |   |
| 11 | Rodriguez-Bano 2010 <sup>72</sup> | 10/04-01/06 | Prospective cohort                         | Mort. cases=17%<br>Mort. controls= 8%   | Spain             | 14 days                             | hosp, time period                                 | 95 cases<br>188 controls | no data   | patients with community onset infection   |
| 12 | Kang 2010 <sup>73</sup>           | 09/08-04/09 | Retrospective cohort                       | Mort. cases=15%<br>Mort. controls= 7.6%<br>OR=2.99; 95%CI(1.01–8.84)                        | Republic of Korea | 30 days                             | none  | 82 case<br>783 controls  | no data   |   |
| 13 | Garcia-Hernandez <sup>74</sup>    | 01/06-07/07 | Retrospective and prospective cohort study | a)Mort. cases=35.5%<br>Mort. controls= 16.8%<br>b)Mort. cases=26.5%<br>Mort. controls= 9.2% | Spain             | a)within 7 days<br>b)within 30 days | none  | 34 cases<br>119 controls | mean ( $\pm$ SD)<br>cases=24.3( $\pm$ 22)<br>controls=20.9( $\pm$ 26.7) |   |
| 14 | Denis 2015 <sup>75</sup>          | 01/05-12/09 | Retrospective study                        | Mort. cases=30%<br>Mort. controls= 27%<br>OR=1.23; 95%CI(0.36–4.23)                         | France            | 30 days                             | date of isolation                                 | 41 cases<br>41 controls  | median (range)<br>cases=15 (10-21)<br>controls=11 (7-17)                |   |

|    |                               |             |                                  |   |                   |                         |  |                            |  |   |
|----|-------------------------------|-------------|----------------------------------|---|-------------------|-------------------------|--|----------------------------|--|---|
| 15 | Ha 2013 <sup>76</sup>         | 01/10-05/12 | Retrospective cohort study       | Mort. cases=22.1%<br>Mort. controls= 12.2%<br>OR = 3.01; 95%CI(1.45–6.28)   | Republic of Korea | 30 days                 | underlying condition                   | 95 cases<br>255 controls   | no data  | all patients had cancer   |
| 16 | Kaya 2013 <sup>77</sup>       | 01/07-10/11 | Retrospective case-control study | Mort. cases=36.4%<br>Mort. controls= 27.5%  | Turkey            | hospitaliz              | none                                   | 44 cases<br>69 controls    | no data  |   |
| 17 | Kim 2013 <sup>78</sup>        | 01/07-12/08 | Retrospective study              | Mort. cases=6.7%<br>Mort. controls= 5.5%  | South Korea       | 30 days                 | underlying condition                   | 15 cases<br>72 controls    | no data  | neutropenic patients  |
| 18 | Lambert 2011 <sup>50</sup>    | 01/05-12/08 | Retrospective cohort study       | a)Mort. cases=50%<br>Mort. controls= 40%<br>aHR=1.3; 95%CI(0.8–2.2)<br>b)Mort. cases=47%<br>Mort. controls= 29%<br>aHR=1.4; 95%CI (0.9–2.3) | Eu countries      | hospitaliz              | ICU                                    | 42 cases<br>217 controls   | *median (IQR)<br>cases=18(11-29)<br>controls=17(9-29)    | a)BSI<br>b)pneumonia patients admitted to ICU<br>*from infection to discharge |
| 19 | Leistner 2014 a <sup>79</sup> | 01/08-12/10 | Retrospective cohort study       | Mort. cases=26%<br>Mort. controls=18%   | Germany           | hospitaliz              | none                                   | 115 cases<br>983 controls  | median (range)<br>cases=27 (12-53)<br>controls=15 (8-32) |   |
| 20 | Leistner 2014 b <sup>80</sup> | 01/08-12/11 | Retrospective cohort study       | Mort. cases=25.3%<br>Mort. controls=17.6%   | Germany           | hospitaliz              | none                                   | 178 cases<br>1322 controls | Multiplicative effect<br>cases=1.07<br>controls=0.83     |   |
| 21 | Martelius 2016 <sup>81</sup>  | 01/99-12/13 | Retrospective study              | a)Mort. cases=7.7%<br>Mort. controls= 5.9%<br>b)Mort. cases=14.3%<br>Mort. controls= 11.9%  | Finland           | a) 7 days<br>b) 28 days | Unit, specimen                         | 182 cases<br>2035 controls | no data  |   |
| 22 | Park 2011 <sup>82</sup>       | 01/05-12/10 | Retrospective cohort study       | a) Mort. cases=8%<br>Mort. controls= 6%<br>b)Mort. cases=18%<br>Mort. controls= 8%  | Republic of Korea | a) 7days<br>b) 30days   | community-onset infection, time period | 50 cases<br>100 controls   | no data  | patients with community -onset infection                                      |

|    |                             |             |                                  |   |                |            |                             |                          |  |  |
|----|-----------------------------|-------------|----------------------------------|---|----------------|------------|-----------------------------|--------------------------|--|--|
|    |                             |             |                                  | OR=6.4; 95%CI(0.3–145.5)  |                |            |                             |                          |  |  |
| 23 | Yip 2006 <sup>83</sup>      | 10/94-08/03 | Retrospective study              | Mort. cases=27.3%<br>Mort. controls= 3.9%                               | Hong Kong      | hospitaliz | underlying condition        | 11 cases<br>77 controls  | no data                                | patients were in continuous ambulatory peritoneal dialysis |
| 24 | Van Aken 2014 <sup>84</sup> | 01/11-09/12 | Retrospective case-control study | Mort. cases=9%<br>Mort. controls= 7%                                    |                | 14 days    | time period, study location | 70 cases<br>140 controls | median±SD cases=11±12<br>controls=9±10 |  |
| 25 | Melzer 2007 <sup>85</sup>   | 06/03-11/05 | Retrospective cohort             | Mort. cases=60.9%<br>Mort. controls= 23.7%<br>OR=3.57; 95%CI(1.48-8.60) | United Kingdom | 30 days    | none                        | 46 cases<br>308 controls | median cases=9<br>controls=12          |  |

Table 22: Short extraction table of original articles on UTI mortality of 3GCREC infected patients vs 3GCSEC infected patients

| Nr | Author                          | Study Period | Study type                       | Outcome   | Location         | Period of outcome | Matching                    | Population                | LOS (days)  | Notes   |
|----|---------------------------------|--------------|----------------------------------|---|------------------|-------------------|-----------------------------|---------------------------|---|---|
| 1  | Al-Otaibi 2013 <sup>86</sup>    | 06/09-06/11` | Retrospective case-control study | Mort. cases=8.9%<br>Mort. controls= 0.9%                              | Saudi Arabia     | hospitaliz        | none                        | 113 cases<br>226 controls | no data   | hospitalised and outpatients  |
| 2  | Ena 2006 <sup>87</sup>          | 01/99-12/04  | Retrospective cohort             | Mort. cases=8%<br>Mort. controls= 8%*                                 | Spain            | hospitaliz        | temporal occurrence         | 61 cases<br>61 controls   | no data   | *author reports that death was not attributable                       |
| 3  | Suankratay 2008 <sup>88</sup>   | 01/04-12/06  | Prospective cohort               | Mort. cases=2.9%<br>Mort. controls= 0%*                               | Thailand         | b) 14days         | underlying condition        | 35 cases<br>71 controls*  | no data   | female patient with acute pyelonephritis<br>*controls were EC, KP, PM |
| 4  | Esteve-Palau 2015 <sup>89</sup> | 08/10-07/13  | Matched cohort study             | Mort. cases=10%<br>Mort. controls= 7%<br>OR=8.011; 95%CI(2.48-25.92)* | Barcelona, Spain | 30 days           | sex, age, date of admission | 60 cases<br>60 controls   | mean (±SD) cases=11.6(±1.5)<br>controls=7.5(±0.8) | *Risk of failure within 7 days (R vs S)                               |

|   |                         |             |                                  |  |                   |        |                   |                          |         |  |
|---|-------------------------|-------------|----------------------------------|--|-------------------|--------|-------------------|--------------------------|---------|--|
| 5 | Park 2015 <sup>90</sup> | 01/07-12/13 | Retrospective case-control study | Mort. cases=1.3%<br>Mort. controls= 1.8% | Republic of Korea | 7 days | time of treatment | 75 cases<br>225 controls | no data | patients with community-acquired infection, and acute pyelonephritis |
|---|-------------------------|-------------|----------------------------------|--|-------------------|--------|-------------------|--------------------------|---------|--|

Table 23: Short extraction table of original articles on rectal swab infections mortality of 3GCREC infected patients vs non infected patients

| Nr | Author                   | Study Period | Study type                           | Outcome  | Location         | Period of outcome        | Matching            | Population              | LOS (days)  | Notes   |
|----|--------------------------|--------------|--------------------------------------|--|------------------|--------------------------|---------------------|-------------------------|---|---|
| 1  | Arnan 2011 <sup>91</sup> | 05/06-12/07  | Prospective multicentre cohort study | a)Mort. cases=1.6%<br>Mort. controls= 0%<br>b)Mort. cases=10%<br>Mort. controls= 11% | Barcelona, Spain | a) 7days<br>b)hospitaliz | undelying condition | 63 cases<br>154controls | mean ( $\pm$ SD)<br>cases=30.15 ( $\pm$ 13.70)<br>controls=29.05 ( $\pm$ 12.11) | patients with acute leukaemia undergoing haematopoietic stem cell transplantation, and who received chemotherapy and developed grade IV neutropenia |

Table 24 and Table 25 present the results of studies that include patients with different sites of infection. Almost all the articles specify the number of cases for the different infection sites but they do not report different mortalities based on the infection site. When it was possible, the results are presented differentiating the mortality for each site of infection.

Table 24: Short extraction table of original articles on mortality of CRKP infected patients vs non infected patients for different infection sites

| Nr | Author                              | Study Period | Study type                             | Outcome   | Location | Period of outcome | Matching | Population                               | LOS (days) | Notes |
|----|-------------------------------------|--------------|--|---|----------|-------------------|----------|--|------------|-------|
| 1  | Nicolas-Chanoine 2012 <sup>92</sup> | 11/08-06/09  | Prospective case-control-control study | Mort. resist=12%<br>Mort. sensit=7%<br>Mort. control=5% | France   | hospitaliz        | none     | 152 resist<br>152 sensit<br>152 controls | no data    |       |

|   |                             |             |                                       |   |     |                              |      |   |   |  |
|---|-----------------------------|-------------|---------------------------------------|---|-----|------------------------------|------|---|---|--|
| 2 | Hayakawa 2013 <sup>93</sup> | 02/10-07/11 | Retrospective case-case-control study | a)Mort. resist=5.7%<br>Mort. sensit=3.5%<br>Mort. NI=3.8%<br>OR R vs S= 1.66; 95%CI(0.37–7.34)<br>OR R vs NI=2.33; 95%CI(0.9–6.07)<br>b)Mort. resist=13.7%<br>Mort. sensit=10.2%<br>Mort. NI=7.6%<br>OR R vs S=1.4; 95%CI(0.52–3.75)<br>OR R vs NI=2.36; 95%CI(1.17–4.78) | USA | a) hospitaliz<br>b) 3 months | none | 319 resist<br>58 sensit<br>319 controls | median (IQR)<br>resist=7(4-12)<br>sensit=7(3-20)<br>NI=4(2-6) |  |
|---|-----------------------------|-------------|---------------------------------------|---|-----|------------------------------|------|---|---|--|

Table 25: Short extraction table of original articles on mortality of 3GCREC infected patients vs 3GCREC infected patients for different infection sites

| Nr | Author                         | Study Period | Study type                         | Outcome   | Location          | Period of outcome     | Matching                              | Population                | LOS (days)          | Notes   |
|----|--------------------------------|--------------|------------------------------------|---|-------------------|-----------------------|---------------------------------------|---------------------------|---------------------|---|
| 1  | Pena 2008 <sup>94</sup>        | 01/96-12/03  | Retrospective matched cohort study | a)Mort. cases=16%<br>Mort. controls= 6%<br>b)Mort. cases=25%<br>Mort. controls= 11% | Spain             | a)7 days<br>b)30 days | site of infection, date of admission  | 100 cases<br>100 controls | no data             |   |
| 2  | Kang 2011 <sup>95</sup>        | 09/10-05/11  | Retrospective case-control study   | Mort. cases=7.4%<br>Mort. controls= 2%  | Republic of Korea | 30 days               | none                                  | 108 cases<br>100 controls | no data             | patients with community onset infection   |
| 3  | Maslikowska 2016 <sup>96</sup> | 06/10-04/13  | Retrospective case-control study   | a)Mort. cases=15%<br>Mort. controls= 2%<br>b)Mort. cases=5%<br>Mort. controls= 2%   | Canada            | 14 days               | sex, age, type of inf, bed allocation | 61 cases<br>49 controls   | not specific for EC | a) all cause mortality<br>b) attributable mortality: defined as chart-documented indication of infection contributing to the cause of death |

This literature research produced a large amount of results, but not all of them fulfilled our selection criteria. Information on mortality is often published, but this was not specific for *Escherichia coli*: they were pooled for Enterobacteriaceae, or for *Escherichia coli* and *Klebsiella pneumoniae* together.

Many studies were excluded because they did not report a comparison group. Several studies referred to genetic analyses and were not eligible for the purposes of this review. All studies were performed in healthcare settings, though some of them report cases of infection that originated in the community or that had onset in the community.

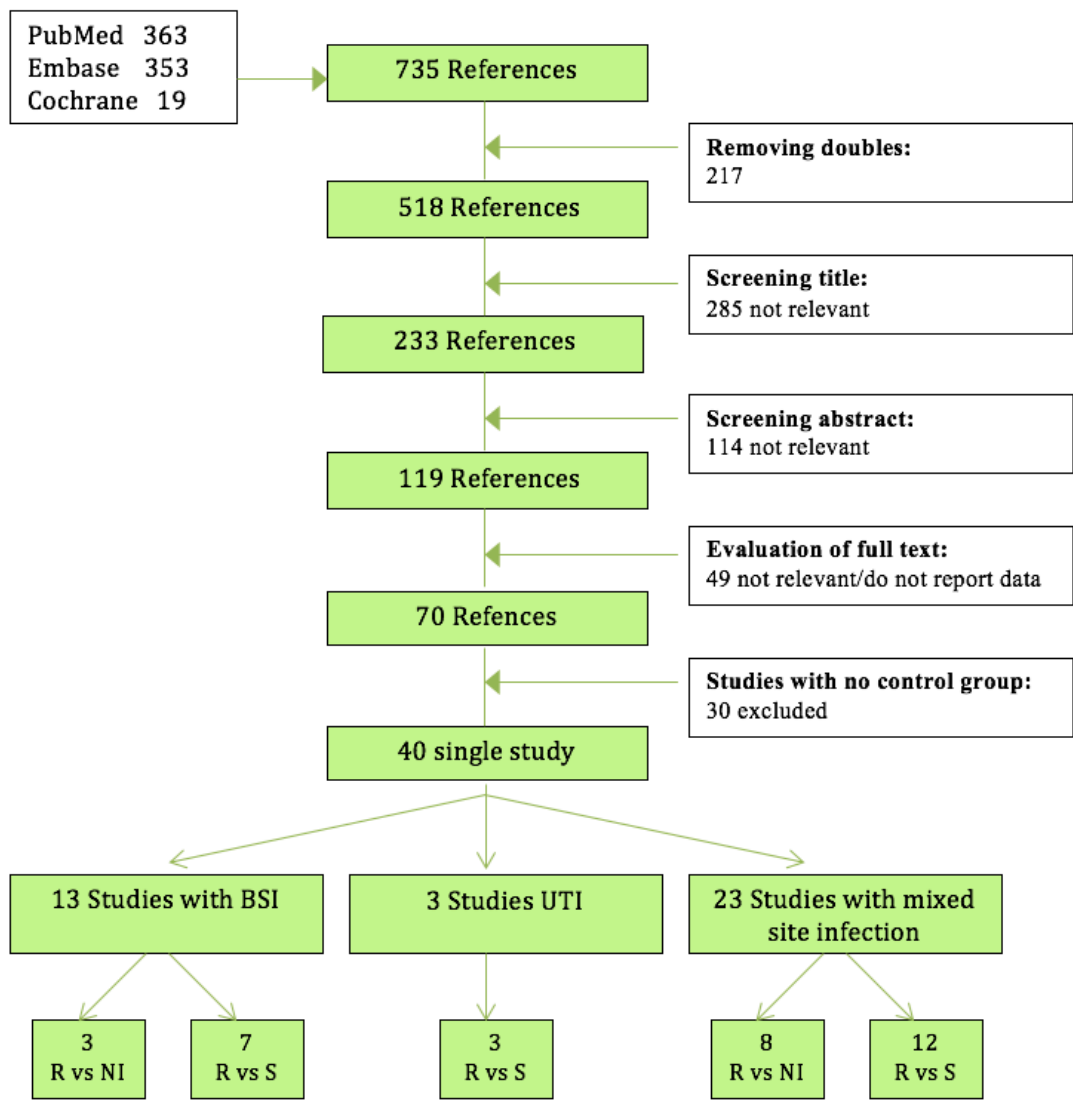
## 7. Carbapenem resistant *Klebsiella pneumoniae*

To research the attributable case fatality and the attributable LOS to carbapenem resistant *Klebsiella pneumoniae* (CRKP) we performed an advanced search on Pubmed using mesh term “*Klebsiella pneumoniae*” and all fields “carbapenem resistant”. Embase was searched for “carbapenem resistant *klebsiella pneumoniae*”. An advanced search on the Cochrane Library was performed using terms “*klebsiella pneumonia*” and “carbapenem”. No language restrictions were made, and a filter for research in humans was applied.

Once identified the studies reporting relevant data, these were grouped based on the site of infection. The majority of them reported mixed samples, as for example blood and urine, blood and bronco-specimens, etc.



Figure 7: Search for studies on carbapenem-resistant *Klebsiella pneumoniae*. Inclusion and exclusion diagram.



From the 13 studies focusing on BSI, 10 were eligible for our purposes. 3 studies were discarded because the comparison was different from those in our inclusion criteria. The same was applied to the studies with mixed site of infection.

In the results were also included 3 systematic review of the literature studies<sup>97-99</sup> of which;

- 1 reported a meta-analysis of data<sup>97</sup>
- 2 reported results for bacteraemia<sup>97,98</sup>,
- 1 does not specify the infection site<sup>99</sup>

All 3 reviews considered CSKP infected patients as a comparison group. Those considering bacteraemia were included in the results for BSI in the R vs S group. References included in the systematic reviews were examined in order to include primary studies if they were missed by our initial search. The published results of 2 systematic reviews are also reported in the tables below.

The following tables include studies reporting results for BSI and UTI from CRKP, based on the comparison group they used. All information is reported as was presented in the original papers.

Table 26: Short extraction table of original articles on BSI mortality of CRKP infected patients vs non infected patients

| Nr | Author                        | Study Period | Study type                         | Outcome  | Location            | Period of outcome | Population               | Matching criteria                          | LOS (days)                                   | Notes   |
|----|-------------------------------|--------------|------------------------------------|--|---------------------|-------------------|--------------------------|--|--|---|
| 1  | Borer 2009 <sup>100</sup>     | 10/05-10/08  | Matched retrospective study        | Mort. cases=71.9%<br>Mort. controls=21.9%<br>RR=3.3; 95%CI(2.9-28.5) | Beer-Sheva Israel   | hospitaliz        | 32 cases<br>32 controls  | *  | median:<br>cases=21<br>contr=18              |   |
| 2  | Gallagher 2014 <sup>101</sup> | 06/05-10/10  | Case-case-control study            | Mort. cases= 45%<br>Mort. contr= 18%<br>OR=3.8; 95%CI(1.4-9.9)       | Philadelphia USA    | hospitaliz        | 43 cases<br>154 controls | **<br>controls are hospitalized for >= 72h | mean:<br>cases=54<br>contr=19.5              | -controls are patients hospitalized for >= 72h  |
| 3  | Mouloudi 2014 <sup>102</sup>  | 01/08-12/11  | Observational matched cohort study | Mort. cases=82.7%<br>Mort. contr=32%                                 | Thessaloniki Greece | hospitaliz        | 17 cases<br>34 controls  | Liver transplant                           | median (range):<br>cases=28(10-64)<br>in ICU | -patients are liver transplant recipients<br>-controls had also live transplant but no KP infection |

\* Hospitalization period, LOS, Charlson comorbidity index, McCabe score, underlying disease, age and sex

\*\* same month/year of occurrence and same medical unit

Table 27: Short extraction table of original articles on BSI mortality of CRKP infected patients vs CSKP infected patients

| Nr | Author                     | Study Period | Study type              | Outcome   | Location | Period of outcome            | Population   | LOS (days) | Notes   |
|----|----------------------------|--------------|-------------------------|---|----------|------------------------------|--------------|------------|---|
| 1  | Falagas 2014 <sup>97</sup> | until 04/12  | Review<br>Meta-analysis | Attribut. mort.= 26-44%<br>in 7 studies<br>Attribut. mort. = (-3)-(-4)%<br>in 2 studies<br>RR=2.05; 95%CI(1.56–2.69)* | World    | different based on the study | 985 patients | no data    | * referred to all 9 studies<br>** only 6 BSI studies<br>*** remaining 3 (not BSI/mixed site of infection) studies |

|   |                               |             |                                  |  |                     |   |                           |  |   |
|---|-------------------------------|-------------|----------------------------------|--|---------------------|---|---------------------------|--|---|
|   |                               |             |                                  | RR 2.19; 95%CI(1.82–2.63)**<br>2RR=1.46; 95%CI(0.47–43.49)***  |                     |   |                           |  |   |
| 2 | Mouloudi 2010 <sup>103</sup>  | 01/07-12/08 | Nested case-control study        | a) Mort.cases= 56.8%<br>Mort. contr= 41%<br>b) Mort. cases= 67.6%<br>Mort. contr= 41%<br>Mort. cases= 27%<br>Mort. contr= 14%                          | Thessaloniki Greece | a) mortality in ICU<br>b) mortality in hospital<br>c) attributable mortality* | 37 cases<br>22 controls   | median(range):<br>total=26 (8-90) in ICU                                       | *within 24h from infection or with infection symptoms despite appropriate therapy |
| 3 | Simkins 2014 <sup>104</sup>   | 06-10       | Case-control study               | Mort. cases= 46%<br>Mort. contr= 0%  | New York, USA       | 6.5 months  | 13 cases<br>39 controls   | no data  | -patients are kidney transplant recipients  |
| 4 | Viale et 2013 <sup>98</sup>   | 1977-2012   | Review                           | Crude mortality rates =20-70%<br>Attribut. mort. patients:<br>-hematologic=75%<br>-ICU=11%<br>-transplant=7%<br>-LTC=5%<br>-medicine=2%<br>-surgery=2% | Italy               |   |                           | median time in developing CRKP infections in hospital (range): cases=14(0-152) | -it is a review not a meta-analysis<br>-good source of references.                |
| 5 | Hussein 2013 <sup>105</sup>   | 01/06-12/08 | Retrospective case-control study | Mort.cases= 43.7%<br>Mort.contr= 29%   | Haifa, Israel       | 30 days   | 103 cases<br>214 controls | median (range):<br>cases=17(1-125)<br>controls=12(1-202)                       |   |
| 6 | Ben-David 2012 <sup>106</sup> | 01/06-12/06 | Retrospective cohort study       | a)Mort. cases=69%<br>Mort. controls=24%<br>b)Mort. cases=48%<br>Mort. controls=17%   | Sheba, Israel       | a)hospitaliz<br>b)infection-related mortality                                 | 42 cases<br>85 controls   | mean LOS before infection detection<br>±SD: survivors=25±81<br>deceased=27±37  |   |
| 7 | Daikos. 2009 <sup>107</sup>   | 02/04-03/06 | Prospective observational study  | Mort.cases= 42.8%<br>Mort.contr= 16.9%<br>OR=3.95; 95%CI(0.94–16.6)  | Athens, Greece      | 14 days   | 14 cases<br>148 controls  | mean LOS before bacteraemia ±SD:<br>both groups=25.85 ± 37.87                  | -all patients were infected with VIM-1-producing KP                               |

Table 28: Short extraction table of original articles on UTI mortality of CRKP infected patients vs CSKP infected patients

| Nr | Author                         | Study Period | Study type                 | Outcome  | Location          | Period of outcome | Population                | Matching                                  | LOS (days)                                      | Notes  |
|----|--------------------------------|--------------|----------------------------|--|-------------------|-------------------|---------------------------|---|---|--|
| 1  | Brizendine 2015 <sup>108</sup> | 2006-2012    | Retrospective cohort study | Mort. cases=18%<br>Mort. contr.=2%                               | Cleveland, USA    | hospitaliz        | 22 cases<br>64 controls   | Patients had solid organ transpalantation | median: cases=7<br>contr=1                      | 4/22 cases died<br>1/64 controls died<br>-controls are susceptible |
| 2  | Pouch 2015 <sup>109</sup>      | 01/07-12/10  | Case-control study         | Mort. cases=30%<br>Mort. contr.=10%<br>HR=3.0;<br>95%CI(1.0–9.0) | New York, USA     | not defined       | 20 cases<br>252 controls  | patients had kidney transplantation       | median(IQR): cases=17(9-43)<br>controls=7(5-10) | -patients are kidney transplant recipients                         |
| 3  | Shilo 2013 <sup>110</sup>      | 01/06-04/09  | Case-control study         | Mort. cases=29%<br>Mort. contr.=25%                              | Jerusalem, Israel | hospitaliz        | 135 cases<br>127 controls |   | mean±SD cases=28±33<br>controls=22±28           | -controls are CSKP producing ESBL                                  |

In the study of Brizendine et al.<sup>108</sup>, 7 case patients (32%) and 8 control patients (13%) had also bacteraemia of CRKP. Pouch et al.<sup>109</sup> reported in their study that 15% of cases and 3% of controls developed bacteraemia within 14 day of bacteriuria onset, while the study of Shilo et al.<sup>110</sup>, 3 patients (4%) in both groups had also bacteraemia. These cases were not excluded from the results displayed in table 28. In Pouch et al. 2 deaths in the cases group followed CRKP sepsis, while none of the deaths in the control group was related to CSKP sepsis.

Table 29 and Table 30 present the results of studies that include patients with different sites of infection. Almost all the articles specify the number of cases for the different infection sites but they do not report different mortalities based on the infection site. When it was possible the results are presented differentiating the mortality for each site of infection.

Table 29: Short extraction table of original articles on mortality of CRKP infected patients vs non infected patients for different infection sites

| Nr | Study | Study Period | Study type | Outcome | Location | Period of outcome | Population | Matching | LOS (days) | Notes |
|----|-------|--------------|------------|---------|----------|-------------------|------------|----------|------------|-------|
|----|-------|--------------|------------|---------|----------|-------------------|------------|----------|------------|-------|

|   |                                |             |                            |   |                      |                          |  |   |  |  |
|---|--------------------------------|-------------|----------------------------|---|----------------------|--------------------------|--|---|--|--|
| 1 | Giannella 2014 <sup>111</sup>  | 06/11-06/13 | Matched case-control study | a)Mort cases=0%<br>Mort. contr.=5%<br>b)Mort. cases=0%<br>Mort. contr.=15%                | Bologna, Italy       | a)30 days<br>b)60 days   | 10 cases<br>20 controls                                    | liver transplant                                | median (range):<br>cases=16(14-27)<br>controls=20(15-62) | -all patients had liver transplant   |
| 2 | Luebbert 2014 <sup>112</sup>   | 09/10-09/11 | Case-control study         | Mort. cases=78%<br>Mort. contr.=11%   | Leipzig, Germany     | 3 months after last case | 9 cases<br>18 controls                                     | liver transplant                                | cases=60<br>controls=32                                  | -patients are liver transplant recipients<br>-controls had also live transplant but not KP infection |
| 3 | Nouvenne 2014 <sup>113</sup>   | 08/11-05/12 | Cross-sectional study      | Mort. cases =21.8%<br>(Mort. Infected=47.5%<br>Mort. Colonized=10.7%)<br>Mort.contr. =15% | Parma, Italy         | hospitaliz               | 133 cases<br>(93 colonized,<br>40infected)<br>400 controls |   | mean±SD<br>cases=35±24<br>controls=18±12                 |  |
| 4 | Bleumin 2012 <sup>114</sup>    | 01/06-06/09 | Nested case-control study  | Mort. cases= 88%<br>Mort. contr.= 52%<br>aHR=5.9; 95%CI(3.2-11.0)                         | Jerusalem, Isreal    | study period             | 43 cases<br>150 controls                                   | -patients had hemodialysis for at least 14 days | no data  | -patients had hemodialysis for at least 14 days  |
| 5 | Debby 2012 <sup>115</sup>      | 05/07-04/08 | Prospective cohort study   | Mort. cases=45.8%<br>Mort. contr.=38.6%   | Tel Hashomer, Israel | hospitaliz               | 48 cases<br>132 controls                                   |   | mean±SD<br>cases=6.06±1.2<br>3 controls=8.39±1.49        | -the cases acquired the infection in the hospital  |
| 6 | Schwaber 2008 <sup>116</sup>   | 2003-2006   | Case-case-control study    | Mort. rate cases=44%<br>Mort. rate controls=2%<br>OR=6.7; 95%CI(2.4-18.8)                 | Tel-Aviv, Israel     | hospitaliz               | 48 CRKP<br>59 controls                                     |   | median (IQR):<br>cases=19 (9-38)<br>controls=2 (1-4)     |  |
| 7 | Pereira 2015 <sup>117</sup>    | 01/10-01/13 | Retrospective cohort study | Mort. rate cases=45%<br>Mort. rate contr.=7%<br>R vs NI: HR=6.92;<br>95%CI(3.24-14.79)    | New York, USA        | 1 year from transplant   | 20 CRKP<br>248 controls                                    | -patients had liver transplant                  | Median (range):<br>cases=40(23-82)<br>controls=12 (9-21) | -patients are liver transplant recipients  |
| 8 | Kofteridis 2014 <sup>118</sup> | 01/09-12/11 | Case-case-control study    | Mort. rate cases=27%<br>Mort. rate contr=4%   | Heraklion, Greece    | not defined              | 83 cases<br>161 controls                                   | no data   | none   |  |

Table 30: Short extraction table of original articles on mortality of CRKP infected patients vs CSKP infected patients for different infection sites

| Nr | Study                            | Study Period | Study type                       | Outcome  | Location          | Period of outcome     | Population               | LOS (days)   | Matching                                  | Notes                                       |
|----|----------------------------------|--------------|----------------------------------|--|-------------------|-----------------------|--------------------------|--|---|---|
| 1  | Candevir Ulu 2015 <sup>119</sup> | 01/12-12/12  | Retrospective cohort study       | Mortality cases=44,7%<br>Mortality contr.=51%                                | Adana, Turkey     | hospitaliz            | 47 cases<br>51 controls  | mean:<br>cases=37.3<br>contr.=29.94<br>median:<br>cases=19<br>contr.=11                | none                                      |   |
| 2  | Dizbay 2014 <sup>120</sup>       | 2004-2010    | Retrospective study              | Mortality cases=57.1%<br>Mortality contr.=27.4%                              | Turkey            | not defined           | 42 cases<br>798 controls | mean<br>cases=38.27<br>contr.=28.17  | none                                      | -cases had nosocomial infections<br>- K spp |
| 3  | Hoxha 2016 <sup>121</sup>        | 12/12-07/13  | Matched cohort study             | a)Attribut. mort.= 16%<br>b)Attribut. mort.= 41%<br>mIRR=3.0; 95%CI(1.3-7.1) | Italy             | a)6 days<br>b)30 days | 49 cases<br>49 controls  | no data  | Age,<br>infection site<br>hospital        |   |
| 4  | Jiao 2015 <sup>122</sup>         | 01/10-12/11  | Retrospective case-control study | Mort. cases=33.6%<br>Mort. contr.=16.6%                                      | Shangai, China    | hospitaliz            | 30 cases<br>30 controls  | mean:<br>cases=33.8<br>controls=18   | none                                      |   |
| 5  | Kofteridis 2014 <sup>118</sup>   | 01/09-12/11  | Case-case-control study          | Mort. rate cases=27%<br>Mort. Rate contr.=15%                                | Heraklion, Greece | not defined           | 83 cases<br>79 controls  | no data  | none                                      |   |
| 6  | Patel 2008 <sup>123</sup>        | 07/04-06/06  | Matched case-case study          | Mort. cases=48%<br>Mort. contr.=26%<br>OR=4.69; 95%CI(1.9–11.58)             | New York, USA     | hospitaliz            | 99 cases<br>99 controls  | mean±SD<br>cases=25.19±24.9<br>controls=6.44±10.1<br>median:<br>cases=21<br>controls=1 | Inf. site                                 |   |
| 7  | Correa 2013 <sup>124</sup>       | 01/06-08/08  | Matched case-control study       | Mort. cases=50%<br>Mort. contr.=27.5%  | Sao Paulo, Brazil | hospitaliz            | 20 cases<br>40 controls  | mean:<br>cases=45.5<br>controls=27   | Inf. date, inf. site, unit where acquired |   |

|    |                                  |                                 |   |  |                          |                        |  |   |  |  |
|----|----------------------------------|---------------------------------|---|--|--------------------------|------------------------|--|---|--|--|
| 8  | CDC Atalanta 2011 <sup>125</sup> | 04/09-02/11                     | Matched case-case study                     | Mortality cases=5%<br>Mortality controls=8%  | West Virginia, USA       | hospitaliz             | 19 cases<br>38 controls  | mean:<br>cases=11.4<br>controls=7.4   | Age, data of sample collection         | -cases likely arrived at the hospital with the infection |
| 9  | Schwaber 2008 <sup>116</sup>     | 2003-2006                       | Case-case-control study                     | Mort. rate cases=44%<br>Mort. rate contr.=12.5%<br>OR=5.4; 95%CI(1.7-17.1)   | Tel-Aviv, Israel         | hospitaliz             | 48 CRKP<br>56 controls   | median (IQR):<br>cases=19(9-38)<br>controls= 1 (1-8)                                | none                                   |  |
| 10 | Falagas 2007 <sup>126</sup>      | 10/00-04/06 *<br>10/03-04/06 ** | Matched case-control study                  | Mortality cases=30.1%<br>Mortality controls=33.9%  | Athens and Crete, Greece | hospitaliz             | 53 cases<br>53 controls  | mean±SD<br>cases=21.4±23.9<br>contr.=15.3±19.9                                      | Age, LOS, inf. site, year of admission | *Athens<br>**Crete                                       |
| 11 | Pereira 2015 <sup>117</sup>      | 01/10-01/13                     | Retrospective cohort study                  | Mort. rate cases=45%<br>Mort. rate contr.=28%  | New York, USA            | 1 year from transplant | 20 CRKP<br>36 controls   | Median (range)<br>CRKP=40(23-82)<br>CSKP=12 (9-21)                                  | none                                   | -patients are liver transplant recipients                |
| 12 | Hauck 2016 <sup>127</sup>        | 12/11-09/14                     | Prospective multicenter observational study | Mort.rate BSI=38%<br>aHR=2.59; 95%CI(1.52-4.50)<br>Mort.rate Pneu=34%<br>aHR=3.44; 95%CI(1.80-6.48)<br>Mort.rate UTI=7%<br>aHR=0.68; 95%CI(0.30-1.45)<br>Mort.rate contr.=9% | San Diego, USA           | hospitalization        | 260 cases:<br>(90 BSI, 49 pneumonia, 121 UTI)<br>223 controls* | median (IQR)<br>BSI=14 (9-24)<br>Pneu=19 (10-30)<br>UTI=10 (6-17)<br>contr=9 (5-16) | none                                   | *R vs CRKP urinary colonization                          |

\* controls had CRKP urinary colonization

All studies were performed in healthcare settings, though some of them report cases of infection that might have been originated in other settings.

Comparing our review with the systemic review of the literature published by the World Health Organisation (WHO) in 2014<sup>128</sup>, we detected more recent publications (2014-2016). The WHO report includes studies comparing with CSKP, while we also included NI as a comparator.

We excluded two studies reported in the WHO review as they did not agree with our eligibility criteria. Daikos et al. 2007<sup>129</sup> defined cases as VIM-1-producing *K. pneumoniae* but did not test the samples for carbapenem resistance, while Lee et al. 2012<sup>130</sup> defined cases as non-susceptible (intermediately susceptible or resistant) to carbapenem.

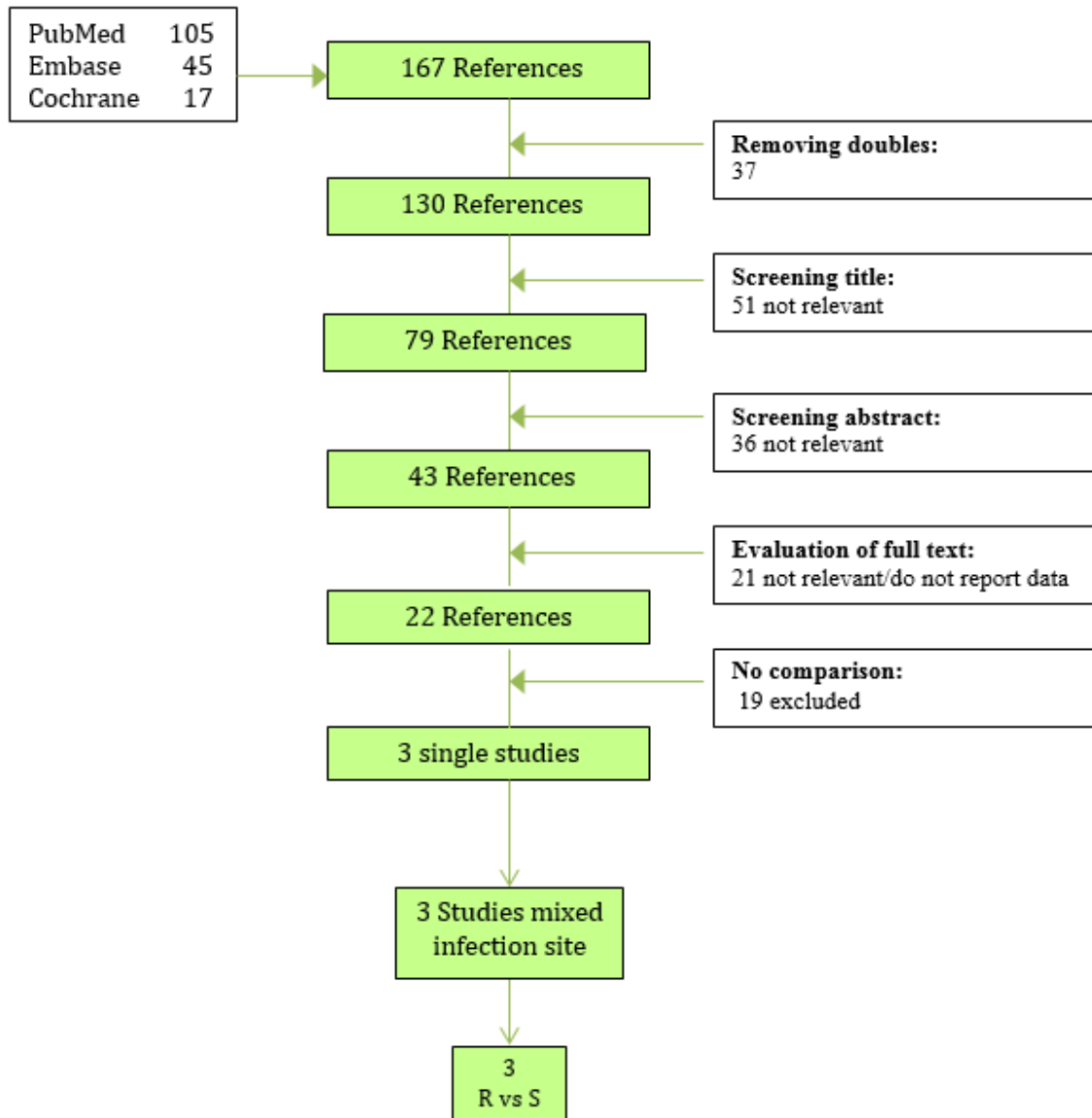
## 8. Colistin resistant *Klebsiella pneumoniae*

To research the attributable case fatality and the attributable LOS to colistin resistant *Klebsiella pneumoniae* (CoRKP) we performed 2 advanced searches on Pubmed using once the mesh term “*Klebsiella pneumoniae*” AND all fields “colistin resistant”, and the second time the mesh term “*Klebsiella pneumoniae*” AND all fields “colistin resistance”. Embase was searched for ‘*Klebsiella pneumoniae*’ AND ‘colistin resistance’, and for ‘*Klebsiella pneumoniae*’ AND ‘colistin resistant’. An advanced search on the Cochrane Library was performed using terms “*Klebsiella pneumoniae*” AND “colistin”. No language restrictions were made, and no filters were applied.

The flow diagram, presented in Figure 8 describes the steps in the literature review of colistin resistant *Klebsiella pneumoniae* infections. The results obtained using the two different key words in PubMed and Embase were aggregated.



Figure 8: Search for studies on colistin resistant *Klebsiella pneumoniae*. Inclusion and exclusion diagram.



The following table includes studies reporting mortality data for CoRKP. All information is reported as was presented in the original papers.

Table 31: Short extraction table of original articles on mortality of CoRKP infected patients vs CoSKP infected patients for mixed site of infection

| Nr | Author                       | Study Period | Study type                    | Outcome  | Location        | Period of outcome | Population              | LOS (days)   | Matching       | Notes                                 |
|----|------------------------------|--------------|-------------------------------|--|-----------------|-------------------|-------------------------|--|----------------|---------------------------------------|
| 1  | Marchaim 2010 <sup>131</sup> | 09/08-08/09  | Case-cohort Study             | Mort. rate cases=40%<br>Mort. rate controls=26%  | Detroit, USA    | hospitaliz        | 5 cases<br>60 controls  | Mean±SD<br>Cases=33±23<br>Controls=30±23           | none           | Outbreak patients, controls were CRKP |
| 2  | Zarkotou 2010 <sup>132</sup> | 04/08-06/09  | Matched Case-Control Study    | Mort. rate cases=69.2%<br>Mort. Rate controls=35.9%<br>Mort. Attributed to KPC-KP* =37.5% in both groups | Piraeus, Greece | hospitaliz        | 13 cases<br>39 controls | Mean±SD<br>Cases= 20.5±20.8<br>Controls= 16.4±12.3 | Infection site | *not explained how was defined        |
| 3  | Capone 2013 <sup>133</sup>   | 12/10-05/11  | Multicentre Prospective Study | Mort. rate cases=40.6%<br>Mort. rate controls=20.3%  | Rome, Italy     | hospitaliz        | 35 cases<br>62 controls | Not specific                                       | none           | all patients were CRKP                |

The following table reports an article identified after the review was concluded, but we report it since it fulfils our eligibility criteria. The article from Rojas et al.<sup>134</sup>, studied patients with CoRKP and CoSKP infection in different site of infection.

Table 32: Short extraction table of original articles on mortality of CoRKP infected patients vs CoSKP infected patients for mixed site of infection

| Nr | Author               | Study Period | Study type                      | Outcome  | Location | Period of outcome | Population               | LOS (days)  | Matching | Notes   |
|----|----------------------|--------------|---------------------------------|--|----------|-------------------|--------------------------|---|----------|---|
| 1  | Rojas <sup>134</sup> | 12/11-10/14  | Prospective nested cohort study | Mort. rate cases=51%<br>Mort. rate controls=39%<br>aHR(95%CI)=3.48 (1.77-6.57) p<0.001 | USA      | 30 days           | 31 cases<br>215 controls | Median(IQR)<br>Cases=8(5-12)<br>Controls=13(7-26) | none     | All samples were resistant to carbapenems too |

Between the non-eligible articles, many reported mortality data for CoRKP infections in a group of selected patients without a comparison group. In these studies<sup>28,135-139</sup> the overall case fatality for the CoRKP infected patients ranged between 20 and 100%. Similar results were reported also in the review of Ah et al. in 2014<sup>140</sup>, while the infection related deaths for CoRKP infected patients in range between 25-71%.

Many papers reported outbreak studies or characterization of the CoRKP bacteria, and few of them included data on mortality. We excluded the majority of studies reporting mortality data because they did not report a comparison group.

The colistin resistant *Klebsiella pneumoniae* infections are a relative new research topic, and there is a lot of interest on studying them. Many studies on the risk factor and the mortality rate of the infections are published, but few of them try to estimate the attributable mortality or the attributable length of stay of this resistance.

## 9. Third-generation Cephalosporin resistant *Klebsiella pneumoniae*

The resistance to the 3<sup>rd</sup> generation of cephalosporin is due to the production from the bacteria of extended-spectrum beta-lactamase enzymes (ESBL). These enzymes can deactivate extended spectrum (3<sup>rd</sup> generation) cephalosporins (e.g., ceftazidime, cefotaxime, and ceftriaxone) and monobactams (e.g., aztreonam).

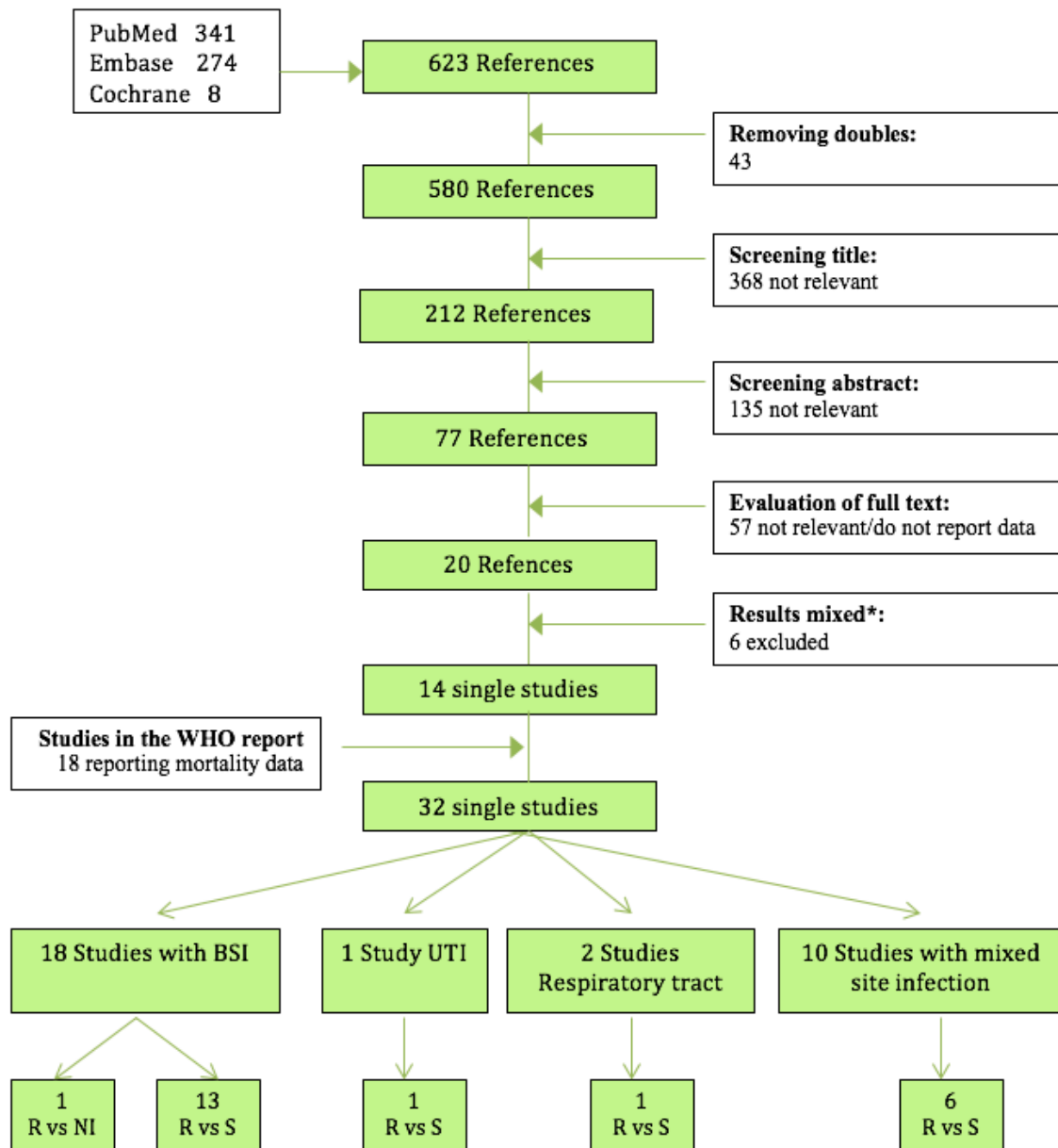
The guidelines internationally accepted for the detection of ESBL-producing bacteria, including *K. pneumoniae*, have been defined in 1999 by the US-based National Committee for Clinical Laboratory Standards (now the Clinical and Laboratory Standards Institute). For the purpose of this review, 3<sup>rd</sup> generation cephalosporin resistant *Klebsiella pneumoniae* (3GCRKP) and ESBL producing *Klebsiella pneumoniae* (ESBL-KP) will be used to define the same phenomenon.

To research the attributable case fatality and the attributable LOS to third-generation cephalosporin resistant *Klebsiella pneumoniae* (3GCRKP) we performed 2 advanced searches on Pubmed using once the mesh term “*Klebsiella pneumoniae*” AND all fields “third generation cephalosporin”, and the second time the mesh term “*Klebsiella pneumoniae*” AND all fields “ESBL OR extended-spectrum beta lactamase”. Embase was searched for ‘*klebsiella pneumoniae* AND third generation cephalosporin’, and ‘*Klebsiella pneumoniae* AND (ESBL OR extended-spectrum beta-lactamase)’. An advanced search on the Cochrane Library was performed using terms “*klebsiella pneumonia*” AND “third generation cephalosporin”, plus a second search using “*klebsiella pneumoniae*” AND “ESBL OR extended-spectrum beta-lactamase”. No language restrictions were made, and a filter for research in humans was applied.

The flow diagram, presented in Figure 9 describes the steps in the literature review of 3<sup>rd</sup> generation cephalosporin resistant *Klebsiella pneumoniae* infections. The results obtained using ESBL and 3<sup>rd</sup> generation cephalosporin as key words were aggregated. Though we did not apply any language filter, 2 studies were excluded from the final results since they were in Chinese language.

Once identified the studies reporting relevant data, these were grouped based on the site of infection. The majority of them reported BSI infections, even though not all of them had a control group.

Figure 9: Search for studies on 3<sup>rd</sup> generation cephalosporin resistant *Klebsiella pneumoniae*. Inclusion and exclusion diagram.



\*These studies reported results for ESBL-*Enterobacteriaceae* or together for *K. pneumoniae* and *Escherichia coli*

From the 18 studies focusing on BSI, 13 were eligible for our purposes. 5 studies were discarded because the comparison was different from those in our inclusion criteria. The same was applied to the studies for respiratory tract and with mixed site of infection.

We also identified a systematic review of the literature on the crude mortality of ESBL-KP infections (Viale et al<sup>98</sup>), which did not consider a comparison group. The crude mortality rate for a BSI infections of ESBL-KP in this review ranged between 14.1% and 43.3%. The following tables include studies reporting results for BSI, UTI and respiratory tract from 3GCRKP, based on the comparison group they used. All information is reported as was presented in the original papers

Table 33: Short extraction table of original articles on BSI mortality of 3GCRKP infected patients vs non infected patients

| Nr | Author                        | Study Period | Study type              | Outcome   | Location          | Period of outcome | Population                | Matching criteria                          | LOS (days)                   | Notes |
|----|-------------------------------|--------------|-------------------------|---|-------------------|-------------------|---------------------------|--|------------------------------|-------|
| 1  | Gallagher 2014 <sup>141</sup> | 06/05-10/10  | Case-case-control study | Mort. rate cases=32%<br>Mort. rate contr.=13%<br>OR=3.6; 95%CI(1.2 to 10.5) | Pennsylvania, USA | hospitaliz        | 111 cases<br>111 controls | Month and medical unit, min 72h hospitaliz | mean cases=63<br>controls=20 |       |

Table 34: Short extraction table of original articles on BSI mortality of 3GCRKP infected patients vs 3GCSKP infected patients

| Nr | Author                         | Study Period | Study type                       | Outcome  | Location     | Period of outcome                             | Population              | LOS (days)                                 | Notes  |
|----|--------------------------------|--------------|----------------------------------|--|--------------|---|-------------------------|--|--|
| 1  | Lee 2014 <sup>53</sup>         | 01/03-12/09  | Retrospective case-control study | a)Mort. rate cases=33.3%<br>Mort. rate controls=24.2%<br>b)Mort. rate cases=33.3%<br>Mort. rate controls=16.3% | Daegu, Korea | a)30 day mortality<br>b)BSI-related mortality | 9 cases<br>153 controls | not reported                               | community acquired infection, study included also EC results                 |
| 2  | Panhotra 2004 <sup>142</sup>   | 07/01-07/03  | Retrospective case-control study | Mort. rate cases=60%<br>Mort. controls=6.2%  | Saudi Arabia | hospitaliz                                    | 10 cases<br>16 controls | cases=44.2<br>controls=24.1                | hospital acquired infection  |
| 3  | Tumbarello 2006 <sup>143</sup> | 01/99-12/03  | Case-case-control study          | a) Mort. rate cases= 25%<br>Mort. rate controls=11%<br>b) Mort. rate cases=52%<br>Mort. rate controls=29%      | Italy        | a) 7 days<br>b) 21 days                       | 48 cases<br>99 controls | mean ± SD<br>cases=34±20<br>controls=31±17 |  |
| 4  | Marra 2006 <sup>144</sup>      | 01/96-05/01  | Retrospective cohort study       | Mort. rate cases=32%<br>Mort. rate controls=15%  | Brazil       | 15 days                                       | 56 cases<br>52 controls |  |  |
| 5  | Kang 2004 <sup>145</sup>       | 01/98-12/02  | Retrospective cohort study       | Mort. rate cases=60%<br>Mort. rate controls=30%  | South-Korea  | 30 days                                       | 10 cases<br>20 controls |  | patients had spontaneous bacterial peritonitis with advanced liver cirrhosis |

|    |                                    |             |                                  |   |  |            |                           |   |   |
|----|------------------------------------|-------------|----------------------------------|---|--|------------|---------------------------|---|---|
| 6  | Kim BN 2002 <sup>146</sup>         | 07/96-06/00 | Retrospective cohort study       | Mort. rate cases=23%<br>Mort. rate controls=20%   | South-Korea  | hospitaliz | 44 cases<br>118 controls  | Mean cases=39.6<br>controls=23.9                    |   |
| 7  | Ariffin 2000 <sup>147</sup>        | 01/96-12/97 | Retrospective cohort study       | Mort. rate cases=50%<br>Mort. rate controls=13%<br>OR=6.5; 95%CI(1.1-38.6)  | Malaysia   | Hospitaliz | 16 cases<br>15 controls   |   | -patients are children with febrile neutropia                                   |
| 8  | Mosqueda-Gomez 2008 <sup>148</sup> | 01/93-12/02 | Retrospective case-control study | Mort. rate cases=35%<br>Mort. rate controls=26.9%   | Mexico   | Hospitaliz | 17 cases<br>104 controls  | mean cases=20.9<br>controls=15.9                    |   |
| 9  | Szilagyi 2009 <sup>149</sup>       | 01/05-12/08 | Retrospective cohort study       | a)Mort. rate cases=36%<br>Mort. rate controls=23%<br>OR=2.5; 95%CI(1.0-5.4)<br>b)Mort. rate cases=18%<br>Mort. rate controls=18%<br>OR=5; 95%CI(1.5-16.2) | Hungary  | Hospitaliz | 100 cases<br>100 controls | median cases=10.5<br>controls=10                    | a) all cause mort.<br>b)inf. related mort.                                      |
| 10 | Pena 2001 <sup>150</sup>           | 05/93-06/95 | Prospective cohort study         | a)Mort. rate cases=32%<br>Mort. rate controls=24%<br>b)Mort. rate cases=16%<br>Mort. rate controls=14%  | Barcelona, Spain   | Hospitaliz | 49 cases<br>43 controls   |   | -hospital acquires infection<br>a)overall mortality<br>b)attributable mortality |
| 11 | Paterson 2004 <sup>151</sup>       | 01/96-12/97 | International prospective study  | Mort. rate cases=27%<br>Mort. rate controls=23%   | South Africa, Taiwan, Australia, Argentina, the United States, Belgium, and Turkey | 14 days    | 78 cases<br>175 controls  |   |   |
| 12 | Tuon 2010 <sup>152</sup>           | 01/06-01/09 | Cohort study                     | Mort. rate cases=49.2%<br>Mort. rate controls=41.9%   | Brazil   | 30 days    | 63 cases<br>41 controls   | Mean ± SD cases= 52.2 ± 39.6<br>controls=36.0 ±29.4 | patients are older than 12  |
| 13 | Lee 2011 <sup>153</sup>            | 01/02-09/09 | Case-control study               | Mort. rate cases=12.1%<br>Mort. rate controls=16%   | South Korea  | 30 days    | 33 cases<br>219 controls  | Mean ± SD cases=26.5 ± 39.0<br>controls=19.9 ± 42.4 | the infection had community onset   |

Table 35: Short extraction table of original articles on UTI mortality of 3GCRKP infected patients vs 3GCSKP infected patients

| Nr | Author                         | Study Period | Study type                 | Outcome                            | Location       | Period of outcome | Population              | Matching                                 | LOS (days)   | Notes                               |
|----|--------------------------------|--------------|----------------------------|------------------------------------|----------------|-------------------|-------------------------|--|--|-------------------------------------|
| 1  | Brizendine 2015 <sup>154</sup> | 2006-2012    | Retrospective cohort study | Mort. cases=18%<br>Mort. contr.=2% | Cleveland, USA | hospitaliz        | 22 cases<br>64 controls | Patients had solid organ transplantation | Prior to UTI<br>Median (IQR)<br>cases=8(1-14)<br>controls=1(1-4) | patients had solid organ transplant |

Brizendine et al.<sup>108</sup> (Table 35) reports that 4 cases (18%) and 8 controls (13%) had also bacteraemia of ESBL-KP, but these cases were not excluded from the results displayed in table 35.

Table 36: Short extraction table of original articles on respiratory tract infections mortality of 3GCRKP infected patients vs 3GCSKP infected patients

| Nr | Study                   | Study Period | Study type                 | Outcome   | Location | Period of outcome | Population               | Matching | LOS (days)   | Notes                                       |
|----|-------------------------|--------------|----------------------------|---|----------|-------------------|--------------------------|----------|--|---|
| 1  | Loh 2006 <sup>155</sup> | 01/04-12/04  | Retrospective cohort study | Mort. rate cases=21.3%<br>Mort. rate controls=12.4% | Malaysia | hospitaliz        | 47 cases<br>394 controls | None     | Median (IQR)<br>cases=14(8-32)<br>controls=5(3-10) | -community and hospital acquired infections |

Table 37 presents the results of studies that include patients with different sites of infection. Almost all the articles specify the number of cases for the different infection sites but they do not report different mortalities based on the infection site. When possible, results are presented differentiating the mortality for each site of infection.

Table 37: Short extraction table of original articles on mortality of 3GCRKP infected patients vs 3GCSKP infected patients for different infection sites



| Nr | Study                        | Study Period | Study type                 | Outcome   | Location         | Period of outcome | Population              | LOS (days)   | Matching                               | Notes                   |
|----|------------------------------|--------------|----------------------------|---|------------------|-------------------|-------------------------|--|--|-------------------------|
| 1  | Gomes 2006 <sup>156</sup>    | 01/98-12/98  | Retrospective cohort study | Mort. rate cases=20.6%<br>Mort. rate controls=21.3% | Brazil           | 21 days           | 68 cases<br>75 controls | no data  | none                                   |                         |
| 2  | Lin 2003 <sup>157</sup>      | 05/01-09/01  | Case-control study         | Mort. rate cases=27.9%<br>Mort. rate controls=20.9% | Taiwan           | hospitaliz        | 43 cases<br>86 controls | mean(range)<br>cases=45 (0-143)<br>controls=18 0-82)   | type of specimen,<br>date of isolation |                         |
| 3  | Kuo 2007 <sup>158</sup>      | 01/00-10/05  | Case-control study         | Mort. rate cases=15%<br>Mort. rate controls=13%     | Taiwan           | 30 days           | 54 cases<br>54 controls | Mean ± SD<br>cases=34.4 ± 5.2<br>controls=14.3±<br>2.3 | type of specimen,<br>date of isolation |                         |
| 4  | Chiu 2005 <sup>159</sup>     | 01/01-12/01  | Case-control study         | Mort. rate cases=20%<br>Mort. rate controls=12.5%   | Taiwan           | hospitaliz        | 15 cases<br>16 controls | Not reported   | none                                   | patients are<br>in NICU |
| 5  | Huang 2007 <sup>160</sup>    | 01/00-12/02  | Prospective cohort study   | Mort. rate cases=10.5%<br>Mort. rate controls=0%    | China            | 30 days           | 19 cases<br>12 controls | Not reported   | none                                   |                         |
| 6  | BARTF*<br>2002 <sup>24</sup> | 1999         | Survey                     | Mort. rate cases=44%<br>Mort. rate controls=33%     | Brooklyn,<br>USA | hospitaliz        | 9 cases<br>9 controls   | median:<br>cases=20<br>controls=33.5                   | Site of infection                      |                         |

\* Brooklyn Antibiotic Resistance Task Force

The following table reports a study which considers the mortality of BSI infections caused by third-generation cephalosporine resistant (3GCRE) and susceptible (3GCSE) *Enterobacteriaceae*. The bacteria included were *Escherichia coli*, *Klebsiella* spp. and *Proteus* spp. But the results are not separated for each strain. Even though the study is not fully eligible for our purposes we decided to include it in this report because of its methodological value.

Table 38: Short extraction table of original articles on BSI mortality of 3GCRE infected patients vs 3GCSE infected patients vs non-infected (NI)

| Nr | Study                          | Study Period | Study type                             | Outcome   | Location | Period of outcome | Population                              | LOS (days)  | Matching | Notes   |
|----|--------------------------------|--------------|--|---|----------|-------------------|---|---|----------|---|
| 1  | Stewardson 2016 <sup>161</sup> | 01/10-12/11  | Multicentre retrospective cohort study | Mort. rate cases=16.1%<br>Mort. rate controls=10.1%<br>Mort. rate NI=1.7%<br>HR=1.39/1.43/1.63* | Europe   | hospitaliz        | 360 cases<br>2100 controls<br>604797 NI | no specific data, see full-text for modelling values* | none     | * the study models the excess in LOS and mortality between groups proposing 3 models for each |

The terms ESBL and extended-spectrum beta-lactamase are widely used in the literature. Our very broad searching strategy produced 580 unique studies but not all the studies were eligible for our study question. Many of the detected studies were abstracts proposed in congresses and never finalised with a peer reviewed paper. These were not included in the results.

All studies were performed in healthcare settings, though some of them report cases of infection that originated in the community.

## 10. Methicillin resistant *Staphylococcus aureus*

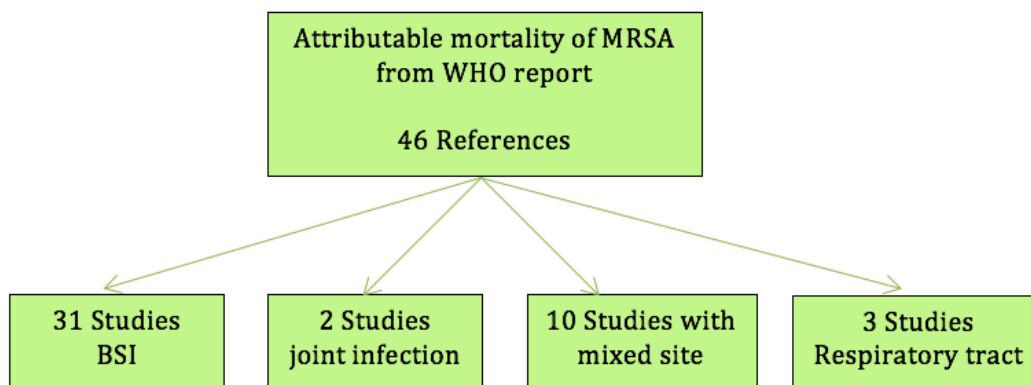
Information on the attributable case fatality and the attributable LOS to methicillin resistant *Staphylococcus aureus* (MRSA), was initially retrieved from the WHO Antimicrobial Resistance Global report on surveillance<sup>162</sup>. We identified the 140 articles included in their literature review, accessed the full text of these papers and extracted the useful data for our study.

The WHO report identifies 46 studies that report the bacterium attributable mortality. The criteria used to classify the deaths due to the infection may vary from study to study, but all the 46 studies considered them as attributable. Some of the studies reported also the all-cause mortality rates for the cases and controls.

The 46 studies are actually 45 unique articles, since one article, Kuint et al. 2007<sup>163</sup>, is reported twice, considering once MRSA cases (which was considered in our review) and the second time multi-drug resistant MRSA. We classified the 45 studies based on the site, Figure 10.1 shows their distributions.

All the studies included a case group of MRSA infected patients and a comparison group of methicillin susceptible *Staphylococcus aureus* (MSSA).

Figure 10.1. Classification of 46 studies that analyse the attributable mortality to MRSA, reported in the WHO Antimicrobial resistance report 2014<sup>162</sup>, based on the site of infection



The WHO report considers that the data of these studies were sufficiently similar and of sufficient quality to include them in meta-analyses. The conclusion of this meta-analysis was the following; "There was a significant increase in bacterium-attributable mortality for patients with MRSA infections (RR 1.64, 95% CI: 1.43 to 1.87,  $P < 0.00001$ )."<sup>162</sup> The absolute effect of MRSA compared to MSSA is 108 more deaths per 1,000 cases (from 73 to 147).

The following tables report the results of the 46 papers based on the site of infection.

Table 39: Short extraction table of original articles on BSI mortality of MRSA infected patients vs MSSA infected patients

| Nr | Author                           | Study Period | Study type                 | Outcome   | Location  | Period of outcome                     | Population                | Matching criteria  | LOS (days)  | Notes                                     |
|----|----------------------------------|--------------|----------------------------|---|-----------|---------------------------------------|---------------------------|--|---|---|
| 1  | Guilarde 2006 <sup>164</sup>     | 01/00-12/01  | Retrospective cohort study | Mort. rate cases=23.5%<br>Mort. rate controls=21.6%   | Brazil    | 30 days                               | 61 cases<br>50 controls   | none   |   |   |
| 2  | Castillo 2012 <sup>165</sup>     | 01/05-12/08  | Multicentre cohort study   | Mort. rate cases=57%<br>Mort. rate controls=46.2%<br>Attribut. mort. cases=71.7%<br>Attribut. mort. controls=57%  | Colombia  | 30 days                               | 186 cases<br>186 controls | hospital, year   | median(IQR) (before BSI)<br>cases=12(2-15)<br>controls=5(1-9)   |   |
| 3  | Lawes 2012 <sup>166</sup>        | 01/06-12/10  | Retrospective cohort study | a)Mort. rate cases=20%<br>Mort. rate controls=17%<br>b)Mort. rate cases=25%<br>Mort. rate controls=21%  | Scotland  | a)30 days<br>b)hospitaliz             | 659 cases<br>208 controls | none   |   |   |
| 4  | Blot 2002 <sup>167</sup>         | 01/92-12/98  | Retrospective cohort study | a)Mort. rate cases=43%<br>Mort. rate controls=16%<br>b)Mort. rate cases=53%<br>Mort. rate controls=18%<br>c)Mort. rate cases=64%<br>Mort. rate controls=24% | Belgium   | a)15days<br>b)30 days<br>c)hospitaliz | 47 cases<br>38 controls   | APACHE II score, diagnostic category                         | (in ICU) mean±SD<br>cases=37±28.7<br>controls=18±16.2<br>median (IQR)<br>cases=28(12-54)<br>controls=14(3-24) |   |
| 5  | Talon 2002 <sup>168</sup>        | 97-98        | Prospective cohort study   | Mort. rate cases=43.3%<br>Mort. rate controls=20.3%   | France    | hospitaliz                            | 30 cases<br>69 controls   | none   | no data   |   |
| 6  | Soriano 2000 <sup>169</sup>      | 01/91-12/98  | Cohort study               | Mort. rate cases=22%<br>Mort. rate controls=9%  | Spain     | hospitaliz                            | 225 cases<br>683 controls | pre-existing comorbidities, underlying disease, LOS, and age | mean<br>cases=18<br>controls=8  | Patients with nosocomial SA bacteraemia   |
| 7  | Selvey 2000 <sup>170</sup>       | 92-97        | Retrospective cohort study | Attribut. mort. rate cases=13.8<br>Attribut. mort. rate controls=8.2%   | Australia | hospitaliz                            | 188 cases<br>316 controls | none   | (prior BSI) median<br>cases=16<br>controls=6  | Inpatients with nosocomial SA bacteraemia |
| 8  | Rubio-Terres 2009 <sup>171</sup> | 01/05-12/05  | Retrospective multi        | a)Mort. rate cases=61.7%<br>Mort. rate controls=56.2%<br>b)Mort. rate cases=29.8%   | Spain     | hospitaliz                            | 121 cases<br>245 controls | none   | mean (95%CI)<br>cases=24.88<br>(19.9–29.9)  | SA bacteraemia patients<br>a) related to  |

|    |                                  |             |                            |  |               |            |                           |                    |   |   |
|----|----------------------------------|-------------|----------------------------|--|---------------|------------|---------------------------|--------------------|---|---|
|    |                                  |             | centre cohort study        | Mort. rate controls=34.4%<br>c)Mort. rate cases=8.5%<br>Mort. rate controls=9.4%                             |               |            |                           |                    | controls=22.66<br>(18.8–26.5)                                     | infection;<br>b)underlying conditions;<br>c)other causes  |
| 9  | Romero-Vivas 1995 <sup>172</sup> | 01/90-09/93 | Prospective cohort study   | Mort. rate cases=58.3%<br>Mort. rate controls=32%  | Spain         | hospitaliz | 84 cases<br>100 controls  | none               | mean cases=32<br>controls=14                                      | N SA bacteraemia patients   |
| 10 | Reshad 1994 <sup>173</sup>       | 01/83-12/91 | Cohort study               | Mort. rate cases=73.9%<br>Mort. rate controls=47.9%  | Japan         | no data*   | 46 cases<br>48 controls   | no data*           | no data*  | Patients with SA septicaemia<br>* not possible to extract the data because the full-text is in Japanese |
| 11 | Quilty 2009 <sup>174</sup>       | 07/04-06/07 | Retrospective audit        | Mort. rate cases=60%<br>Mort. rate controls=40%  | Australia     | no data    | 5 cases<br>5 controls     | Underlying disease | no data   | Chemotherapy-induced febrile neutropenia patients with SA sepsis  |
| 12 | Hakim 2007 <sup>175</sup>        | 01/00-12/04 | Retrospective cohort study | Mort. rate cases=12%<br>Mort. rate controls=0%   | New York, USA | hospitaliz | 14 cases<br>22 controls   | none               | no data   | Bacteraemia in children   |
| 13 | Nickerson 2006 <sup>176</sup>    | 06/03-12/04 | Retrospective cohort study | Mort. rate cases=69%<br>Mort. rate controls=44%<br>*Attribut. mort.=48%                                      | Thailand      | hospitaliz | 36 cases                  | none               | no data   | *it is not defined how it calculated  |
| 14 | Kim 2003 <sup>177</sup>          | 01/98-11/01 | Retrospective cohort study | Mort. rate cases=40%<br>Mort. rate controls=33.3%  | Seul, Korea   | hospitaliz | 127 cases<br>111 controls | none               | (before inf.)<br>mean±SD<br>cases=33.9±34.6<br>controls=17.7±34.3 |   |
| 15 | Melzer 2003 <sup>178</sup>       | 01/95-12/00 | Cohort study               | a)Mort. rate cases=11.8%<br>Mort. rate controls=5.1%<br>b)Mort. rate cases=17.8%<br>Mort. rate controls=8.5% | England, UK   | hospitaliz | 433 cases<br>382 controls | none               | no data   | nosocomial BSI,<br>a)mort. due to inf.<br>b)mort. due to other causes                                   |

|    |                               |             |                                 |  |                     |            |                           |  |  |   |
|----|-------------------------------|-------------|---------------------------------|--|---------------------|------------|---------------------------|--|--|---|
| 16 | Kuint 2007 <sup>163</sup>     | 01/93-12/03 | Retrospective cohort study      | a)Mort.rate cases=9%<br>Mort.rate controls=8%<br>b)Mort. rate cases=27%<br>Mort. rate controls=25%     | Tel Aviv, Israel    | hospitaliz | 11 cases<br>12 controls   | none   | no data  | patients in neonatal ICU<br>a)sepsis related mort.<br>b)all cause mort.                       |
| 17 | Khatib 2006 <sup>179</sup>    | 01/02-12/02 | Prospective observational study | Attribut. mort=12.2%*  | Detroit, USA        | hospitaliz | 174 cases<br>168 controls | none   | no data  | *Attributable mortality was defined as death with positive blood culture or persistent sepsis |
| 18 | Lodise 2005 <sup>180</sup>    | 01/99-01/01 | Retrospective cohort study      | Mort. rate cases=30.6%<br>Mort. rate controls=15.3%  | Michigan, USA       | 30 days    | 170 cases<br>183 controls | none   | mean cases=20.1<br>controls=13.7                                 |   |
| 19 | Nickerson 2009 <sup>181</sup> | 11/06-11/07 | Prospective observational study | Mort. rate cases=68%<br>Mort. rate controls=46%  | Thailand            | 12 weeks   | 27 cases<br>71 controls   | none   | no data  |   |
| 20 | Harbarth 1998 <sup>182</sup>  | 01/89-12/95 | Case-control study              | a)Mort. rate cases=18%<br>Mort. rate controls=24%<br>b)For both groups=34%                             | Geneva, Switzerland | hospitaliz | 38 cases<br>38 controls   | age, LOS, nr. comorbidities, McCabe score, Jackson score | (after BSI) median (range) cases=30(1-141)<br>controls=23(1-178) | a) mort. caused by infection<br>b)all cause mort.   |
| 21 | Cunney 1994 <sup>183</sup>    | 12/91-05/93 | Retrospective cohort study      | Mort. rate cases=22%<br>Mort. rate controls=3%   | Dublin, Ireland     | hospitaliz | 18 cases<br>60 controls   | none   | no data  | hospital acquired inf.  |
| 22 | Das 2006 <sup>184</sup>       | 11/01-12/02 | Prospective cohort study        | a)Mort. rate cases=33%<br>Mort. rate controls=16%<br>b)Mort. rate cases=56%<br>Mort. rate controls=39% | Birmingham, UK      | 3 months   | 84 cases<br>56 controls   | none   | (before BSI) median cases=14<br>controls=8                       | a)attribut. mort<br>b)all cause mort.   |
| 23 | Austin 2003 <sup>185</sup>    | 01/94-01/99 | Matched case-control study      | a)Mort. rate cases=36%<br>Mort. rate controls=20%<br>b)Mort. rate cases=50%<br>Mort. rate controls=69% | Ontario, Canada     | hospitaliz | 50 cases<br>50 controls   | sex, age, primary diagnoses                              | mean cases=44.1<br>controls=33.9                                 | Inpatient bacteraemia<br>a)attribut. mort<br>b)all cause mort.                                |
| 24 | Conterno 1999 <sup>186</sup>  | 01/91-09/92 | Nested case-control study       | *Mort. rate cases=10-90%<br>Mort. rate controls=4-76%  | Brazil              | 14 days    | 90 cases<br>46 controls   | none   | no data  | *the mortality is estimated with predictive models  |

|    |                                 |             |   |   |                 |                           |  |                    |   |   |
|----|---------------------------------|-------------|---|---|-----------------|---------------------------|--|--------------------|---|---|
| 25 | Hill 2008 <sup>187</sup>        | 06/00-12/06 | Cohort study                              | Mort. rate cases=56%<br>Mort. rate controls=30%<br>a)Mort. rate cases=25%<br>Mort. rate controls=67%<br>b)Mort. rate cases=86%<br>Mort. rate controls=100%                                    | Belgium         | 6 months                  | 16 cases<br>56 controls                                    | Underlying disease | no data   | Infective endocarditis<br>a)CA inf.<br>b)antimicrobial therapy due to a contraindication to surgery |
| 26 | Ganga 2009 <sup>188</sup>       | 11/05-12/06 | Prospective observational study           | a)Mort. rate cases=23.9%<br>Mort. rate controls=8.9%<br>b)Mort. rate cases=7.4%<br>Mort. rate controls=2.2%   | Michigan, USA   | hospitaliz                | 163 cases<br>90 controls                                   | none               |   | inpatients with SA bacteraemia<br>a) all cause mort.<br>b) attributable mort.                       |
| 27 | Burke 2009 <sup>189</sup>       | 2001-2006   | Retrospective study                       | Mort. rate cases=10%<br>Mort. rate controls=4%  | California, USA | hospitaliz                | 29 cases<br>121 controls                                   | age                | mean cases=36<br>controls=16.3<br>median(IQR) cases=38(16-73)<br>controls=16(7-42)                        | all patients were children  |
| 28 | de Oliveira 2002 <sup>190</sup> | 90-91/95-96 | Nested case-control study                 | Mort. rate cases=45.9%<br>Mort. rate controls=20.7%   | Brazil          | 14 days                   | 159 cases<br>92 controls                                   | none               | no data   | patients with <14 years   |
| 29 | Lesens 2003 <sup>191</sup>      | 05/01-05/02 | Prospective cohort study                  | Mort. rate cases=34%<br>Mort. rate controls=20.4%   | France          | hospitaliz                | 53 cases<br>113 controls                                   | none               | no data   |   |
| 30 | O'kane 1998 <sup>192</sup>      | 01/93-12/93 | Retrospective study                       | Mort. rate cases=9% *<br>Mort. rate controls=6%*  | Australia       | hospitaliz                | 32 cases<br>73 controls                                    | none               | post infection mean cases=24<br>controls=19   | *directly attributable mortality  |
| 31 | De Kraker 2011 <sup>193</sup>   | 07/07-06/08 | Prospective parallel matched-cohort study | R vs NI (Cohort I)<br>a) Mort. rate resist= 31%<br>Mort. rate NI=8%<br>aOR=4.4<br>b) Mort. rate resist= 36%<br>Mort. rate NI=9%<br>aHR=3.1<br>S vs NI (Cohort II)<br>a) Mort. rate sensit=22% | Europe          | a)30 days<br>b)hospitaliz | I) 248 resistant<br>453 NI<br>II) 618 sensitive<br>1170 NI | LOS                | median (IQR) Cohort I resistant=16 (6-32)*<br>NI=7(3-18)*<br>Cohort II sensitive=15(7-26)*<br>NI=8(4-14)* |   |



|  |  |  |  |   |  |  |  |  |   |  |
|--|--|--|--|---|--|--|--|--|---|--|
|  |  |  |  | Mort. rate NI=8%<br>aOR=2.4<br>b) Mort. rate sensit=23%<br>Mort. rate NI=7%<br>aHR=3.1<br>R vs S<br>a) OR=1.8<br>b) HR= 1.1 |  |  |  |  | excess LOS<br>R vs NI= 9.2*<br>S vs NI= 8.6*<br>R vs S= 0.6 |  |
|--|--|--|--|---|--|--|--|--|---|--|

Table 40: Short extraction table of original articles on joint infections mortality of MRSA infected patients vs MSSA infected patients

| Nr | Author                         | Study Period | Study type                 | Outcome  | Location            | Period of outcome               | Population              | Matching criteria | LOS (days)                     | Notes  |
|----|--------------------------------|--------------|----------------------------|--|---------------------|---------------------------------|-------------------------|-------------------|--------------------------------|--|
| 1  | Salgado 2007 <sup>194</sup>    | 01/95-12/04  | Retrospective cohort study | Mort. rate both=0%   | South Carolina, USA | hospitaliz                      | 31 cases<br>12 controls | none              | Median cases=15<br>controls=10 | Patients with prosthetic joint infection from SA |
| 2  | Al-Nammari 2007 <sup>195</sup> | 06/00-06/05  | Retrospective study        | a)Mort. rate cases=13%<br>Mort. rate controls=5%<br>b)Mort. rate cases=26%<br>Mort. rate controls=7% | England, UK         | a) sepsis related<br>b)6 months | 15 cases<br>43 controls | septic arthritis  | no data                        |  |

Table 41: Short extraction table of original articles on mortality of MRSA infected patients vs MSSA infected patients for different infection sites

| Nr | Author                    | Study Period | Study type                 | Outcome  | Location                    | Period of outcome | Population   | Matchin g criteria | LOS (days) | Notes           |
|----|---------------------------|--------------|----------------------------|--|-----------------------------|-------------------|--|--------------------|------------|-----------------|
| 1  | Rello 2013 <sup>196</sup> |              | Retrospective cohort study | a)Mort. rate cases=60%<br>Mort. rate controls=50%<br>b)Mort. rate cases=33.3%<br>Mort. rate controls=10% | a)Latin America<br>b)Europe | hospitaliz        | a)5 cases<br>6 controls<br>b)15 cases<br>30 controls | VAP                | no data    | patients in ICU |

|   |                                   |                 |  |  |                           |            |                           |                                |   |  |
|---|-----------------------------------|-----------------|--|--|---------------------------|------------|---------------------------|--------------------------------|---|--|
| 2 | Spindel<br>1995 <sup>197</sup>    | 01/87-<br>12/91 | Observational<br>analytical<br>study   | Mort. rate cases=10.7%<br>Mort. rate controls=10%  | Oregon, USA               | hospitaliz | 20 cases<br>48 controls   |                                | mean<br>cases=15<br>controls=12   | Veterans' nursing<br>home, elderly men<br>with severe<br>underlying diseases   |
| 3 | Davis<br>2007 <sup>198</sup>      | 10/03-<br>12/05 | Prospective<br>cohort study            | No death related to<br>infections  | USA                       |            | 102 cases<br>102 controls | none                           |   | Patients with<br>community<br>associated SA<br>infections  |
| 4 | Graffunder<br>2002 <sup>199</sup> | 97-99           | Case-control<br>study                  | a)Attrib. mort. rate<br>cases=8.3%<br>Attrib. mort. rate<br>controls=5.7%<br>b)Mort. rate cases=28.8%<br>Mort. rate controls=19.5% | USA                       | hospitaliz | 121 cases<br>123 controls | none                           | (before culture)<br>mean(range)<br>cases=18.8(2-98)<br>controls=8.4(2-<br>45)                       | nosocomial infection<br>a) to the infection<br>b) all cause  |
| 5 | Priest<br>2005 <sup>200</sup>     | 94-00           | Retrospective<br>case-control<br>study | a)Mort. rate cases=55%<br>Mort. rate controls=4%<br>b)Mort. rate cases=27%<br>Mort. rate controls=0%                               | North<br>Carolina,<br>USA | hospitaliz | 11 cases<br>24 controls   | vertebral<br>osteomy<br>elitis | no data   | Inpatients with SA<br>haematogenous<br>vertebral<br>osteomyelitis<br>a)all cause mort.<br>b)inf. related mort.   |
| 6 | Hershow<br>1992 <sup>201</sup>    | 01/89-<br>12/89 | Retrospective<br>cohort study          | Mort. rate cases=1%<br>Mort. rate controls=0%  | Illinois, USA             | hospitaliz | 22 cases<br>22 controls   | none                           | median<br>cases=14<br>controls=10   | Adults with<br>nosocomial SA<br>infection  |
| 7 | Hulten<br>2010 <sup>202</sup>     | 08/01-<br>07/07 | Retrospective<br>cohort study          | Mort. rate cases=17.2%<br>Mort. rate controls=7.0%*  | Texas, USA                | hospitaliz | 29 cases<br>71 controls   | none                           | mean<br>cases=57.6<br>controls=68.2<br>median(range)<br>cases=29 (3-339)<br>controls=56 (0-<br>158) | patients were<br>children<br>*mortality was<br>calculated just for<br>bacteraemia and<br>catheter associated<br>inf., not all cases and<br>controls of the study |
| 8 | Joo<br>2012 <sup>203</sup>        | 2007-<br>2009   | Matched case-<br>control study         | a)Mort. rate cases=9.5%<br>Mort. rate controls=4.8%<br>b)Mort. rate cases=9.5%<br>Mort. rate controls=3.6%                         | Seul, Korea               | hospitaliz | 84 cases<br>84 controls   | admissio<br>n date             | median(range)<br>cases=20 (2-202)<br>controls=22 (2-<br>158)  | Community-onset SA<br>infection,<br>a) all cause mort.<br>b)inf. Related mort.   |

|    |                              |             |                            |  |                  |            |                          |                         |         |   |
|----|------------------------------|-------------|----------------------------|--|------------------|------------|--------------------------|-------------------------|---------|---|
| 9  | Capitano 2003 <sup>204</sup> | 01/96-08/00 | Retrospective cohort study | Mort. rate cases=10% *<br>Mort. rate controls=10%* | Connecticut, USA | hospitaliz | 41 cases<br>49 controls  | long-term care facility | no data | all patients were in long term care facility<br>* infection related mortality |
| 10 | Clancy 2005 <sup>205</sup>   | 01/02-06/04 | Retrospective cohort study | Mort. rate cases=0%<br>Mort. rate controls=1.5%    | Colorado, USA    | 30 days    | 57 cases<br>136 controls | CA-SA                   | no data | infections were community-acquired  |

Table 42: Short extraction table of original articles on mortality of MRSA infected patients vs MSSA infected patients with respiratory tract infection

| Nr | Author                       | Study Period | Study type                 | Outcome  | Location | Period of outcome                   | Population              | Matching criteria     | LOS (days)  | Notes   |
|----|------------------------------|--------------|----------------------------|--|----------|-------------------------------------|-------------------------|-----------------------|---|---|
| 1  | Rello 1994 <sup>206</sup>    | 01/91-06/93  | Retrospective cohort study | a)Mort. rate cases=61.7%<br>Mort. rate controls=56.2%<br>b)Mort. rate cases=18.1%<br>Mort. rate controls=26.3% | Spain    | hospitaliz                          | 11 cases<br>38 controls | none                  | no data   | patients with VAP<br>a)mort. related to infection; b)mort. non related to infection               |
| 2  | Gonzalez 1999 <sup>207</sup> | 01/90-12/95  | Retrospective cohort study | a)Mort. rate cases=25%<br>Mort. rate controls=14.8%<br>b)Mort. rate cases=56.3%<br>Mort. rate controls=40.7%   | Spain    | a) first 48h<br>b) due to infection | 32 cases<br>54 controls | bacteremic pneumoniae | mean±SD<br>cases=44.4±27.7<br>controls=30.3±21.7                            |   |
| 3  | Pujol 1998 <sup>208</sup>    | 01/90-12/94  | Prospective cohort study   | Mort. rate cases=56.1%<br>Mort. rate controls=37.8%  | Spain    | hospitaliz                          | 41 cases<br>98 controls | Underlying disease    | prior inf.<br>mean±SD<br>cases=26.2±17.7<br>controls=5±6.4*;<br>15.8±13.3** | Mechanically ventilated ICU patients who developed SA pneumonia,<br>*early onset;<br>**late onset |

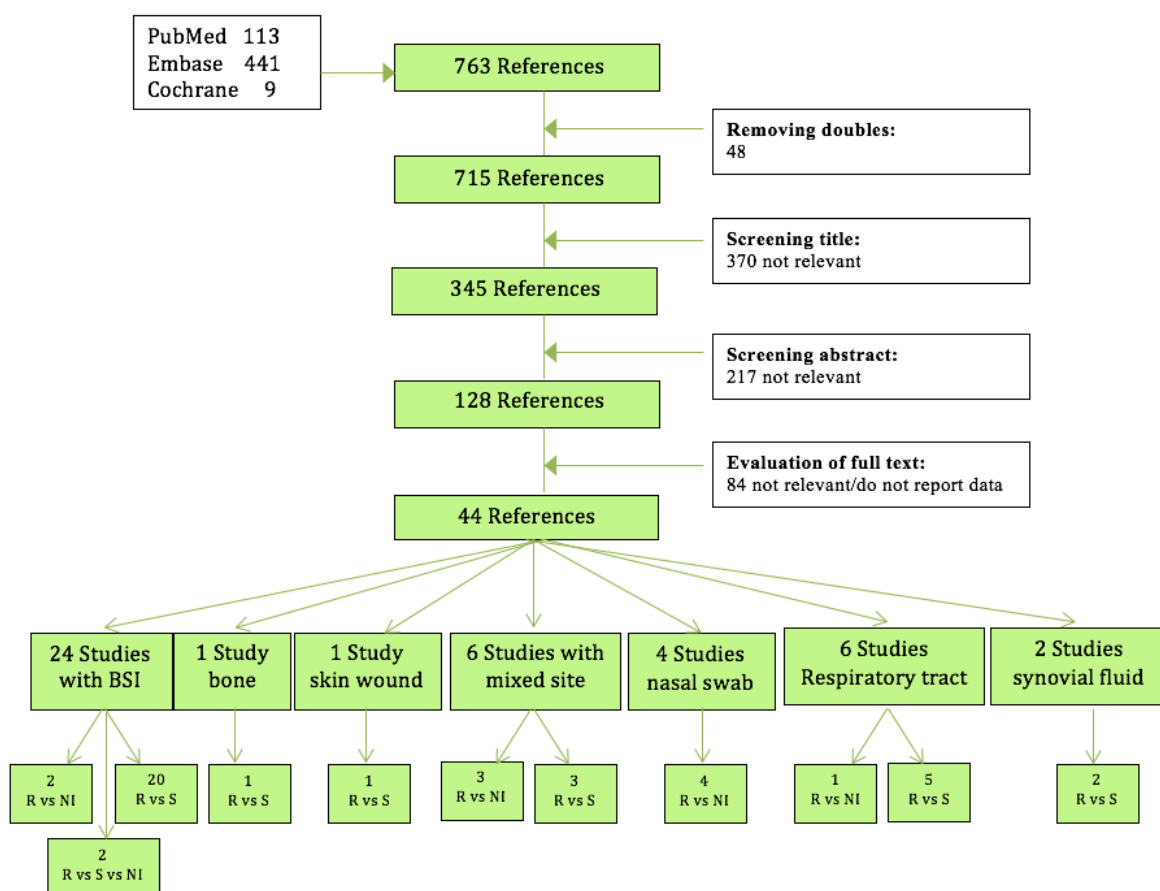
We also performed a separate literature review using time filters from April 2013 up to the 12<sup>th</sup> of December 2016 to detect new articles.

We performed an advanced search on Pubmed using the mesh term “MRSA” AND all fields “mortality”. On Embase was searched for ‘MRSA’ AND ‘mortality’ and an advanced search was performed on the Cochrane Library was performed using terms “MRSA” AND “mortality”. We applied a filter to include only human studies, and included only published articles. No language restrictions were made, and no further filters were applied.

The flow diagram presented in Figure 10.2 describes the steps in the literature review of MRSA infections.

Once identified the studies reporting relevant data, these were grouped based on the site of infection. The majority reported BSI infections, even though not all of them had a control group.

Figure 10.2. Search for studies on MRSA infections. Inclusion and exclusion diagram.



As shown in Figures 10.2., even though we applied a time filter and looked for papers containing the term “mortality”, which makes the research very specific, more than 700 unique papers were detected. After the different exclusion steps the vast majority of them were not eligible for the purposes of our study, but we still could include 44 articles. This is the highest number of eligible articles among all the reviews performed.

The following tables include studies reporting results for the different site of infection based on the comparison group they used. All information is reported as was presented in the original papers.

Table 43: Short extraction table of original articles on mortality of patients with MRSA BSI infections vs non-infected patients

| Nr | Author                       | Study Period | Study type                | Outcome  | Location    | Period of outcome            | Population               | Matching criteria  | LOS (days)   | Notes   |
|----|------------------------------|--------------|---------------------------|--|-------------|------------------------------|--------------------------|--|--|---|
| 1  | Atmaca 2014 <sup>128</sup>   | 01/04-12/11  | Nested case-control study | Mort. rate cases= 47.5%<br>Mort. rate controls=29.3%   | Turkey      | hospitaliz                   | 99 cases<br>99 controls  | BSI, ward, period of time                                | median cases=59<br>controls=8  | data extracted from original paper in Turkish with help of google translate |
| 2  | McMaster 2015 <sup>209</sup> | 04/07-11/13  | Prospective study         | a) Mort. rate cases= 19%<br>Mort. rate controls=21.2%<br>b) Mort. rate cases= 32.8%<br>Mort. rate controls=34.5% | Glasgow, UK | a) hospitaliz<br>b) 180 days | 58 cases<br>174 controls | age, APACHE II, LOS in ICU, surgical/non-surgical status | in ICU median (range) cases=16.6 (1.5-124.1)<br>controls=16.9 (1.9-92.1) | all patients were in ICU  |

Table 44: Short extraction table of original articles on BSI mortality of MRSA infected patients vs MSSA infected patients and vs non infected patients

| Nr | Author                          | Study Period | Study type                             | Outcome  | Location      | Period of outcome | Population                                  | Matching criteria | LOS (days)  | Notes   |
|----|---------------------------------|--------------|--|--|---------------|-------------------|---|-------------------|---|---|
| 1  | Stewards on 2016 <sup>161</sup> | 01/20-12/12  | Multicentre retrospective cohort study | Mort. rate resistant=22.1%<br>Mort. rate sensitive=16.8%<br>Mort. rate NI=1.7%<br>R vs NI:<br>HR*=3.81/2.61/2.42<br>R vs S: HR*=1.19/1.20/1.26 | Europe        | hospitaliz        | 163 resistant<br>885 sensitive<br>604797 NI | none              | no specific data, see full-text for modelling values* | * the study models the excess in LOS between groups proposing 3 models for each |
| 2  | Yasmin 2016 <sup>210</sup>      | 01/12-10/14  | Case-case-control study                | a)Mort. rate resist= 22%<br>Mort. rate sensit=19.5%<br>Mort. rate NI=1.7%<br>b)Mort. rate resist=19.5%<br>Mort. rate sensit=10.3%              | New York, USA | hospitaliz        | 118 resistant<br>145 sensitive<br>118 NI    | date of hosp.     | no specific data                                      | a) mortality during hospitalisation<br>b) attributable mortality                |

Table 45: Short extraction table of original articles on BSI mortality of MRSA infected patients vs MSSA infected patients

| Nr | Author                               | Study Period | Study type                 | Outcome  | Location       | Period of outcome                      | Population   | Matching criteria | LOS (days)  | Notes  |
|----|--------------------------------------|--------------|----------------------------|--|----------------|--|--|-------------------|---|--|
| 1  | De la Calle 2016 <sup>211</sup>      | 01/00-12/14  | Retrospective study        | a) Mort. rate cases= 40.5%<br>Mort. rate controls=37.5%<br>b) Mort. rate cases= 50%<br>Mort. rate controls=44.6%                                   | Spain          | a) 30 days<br>b) infection related     | 42 cases<br>56 controls                                  | pneumonia         | no data   | all patients had bacteremic pneumonia  |
| 2  | De Rosa 2016 <sup>212</sup>          | 2010-2011    | Retrospective study        | Mort. rate cases= 17.9%<br>Mort. rate controls=14.3%   | Italy          | 21 days                                | 106 cases<br>83 controls                                 | BSI               | no data   |  |
| 3  | Deodhar 2015 <sup>213</sup>          | 05/11-06/12  | Prospective study          | Mort. rate cases= 21%<br>Mort. rate controls=21.3%   | India          | hospitaliz                             | 40 cases<br>61 controls                                  | none              | no data   |  |
| 4  | Dolapo 2014 <sup>214</sup>           | 2000-2009    | Retrospective study        | a) Mort. rate cases= 0%<br>Mort. rate controls=9.8%<br>b) Mort. rate cases= 15.7%<br>Mort. rate controls=5.2%                                      | Tennessee, USA | 14 days                                | a) 10 cases<br>31 controls<br>b) 64 cases<br>51 controls | NICU              | mean±SD<br>a) cases=80.6±42.4<br>controls=87.4±40.6<br>b) cases=53.6±36.6<br>controls=55.7±30.2 | patients were in NICU<br>a) period A (2000-2003)<br>b) period B (2004-2009)                        |
| 5  | Fortuin-de Smidt 2015 <sup>215</sup> | 09/12-09/13  | Cross-sectional study      | Mort. rate cases= 29.1%<br>Mort. rate controls=14.3%   | South Africa   | hospitaliz                             | 86 cases<br>154 controls                                 | none              | median (IQR)<br>cases=38 (14–64)<br>controls=19 (7–33)  |  |
| 6  | Kim D.H 2014 <sup>216</sup>          | 06/06-02/11  | Retrospective study        | Mort. rate cases= 62%<br>Mort. rate controls=0%<br>OR=0.158; 95%CI(0.047–0.534)  | Tennessee, USA | hospitaliz                             | 29 cases<br>8 controls                                   | cardiac implant   | no specific data  | all patients had Cardiac Implanted Electronic Device-Related Infective Endocarditis                |
| 7  | Kobayashi 2014 <sup>217</sup>        | 04/04-03/11  | Retrospective cohort study | Mort. rate cases= 39.7%<br>Mort. rate controls=30.7%   | Japan          | 90 days                                | 151 cases<br>189 controls                                | none              | no data   |  |
| 8  | Lee J.Y 2014 <sup>218</sup>          | 01/04-12/12  |                            | 1-a)Mort. rate cases= 3.2%<br>Mort. rate controls=3.6%<br>1-b) Mort. rate cases= 6.5%<br>Mort. rate controls=13.8%<br>1-c) Mort. rate cases= 16.1% | South Korea    | a) 1 week<br>b) 30 days<br>c) 12 weeks | 31 cases<br>138 controls                                 |                   | median (IQR)<br>cases=47 (19–87)<br>controls=24 (14–44.5)                                       | patients had CA-infections<br>1-a/b/c) all-cause mortality<br>2-a/b/c) infection related mortality |

|    |                               |             |                            |   |                         |                          |                           |                                 |   |   |
|----|-------------------------------|-------------|----------------------------|---|-------------------------|--------------------------|---------------------------|---------------------------------|---|---|
|    |                               |             |                            | Mort. rate controls=19.6%<br>2-a) Mort. rate cases= 0%<br>Mort. rate controls=3.6%<br>2-b) Mort. rate cases= 3.2%<br>Mort. rate controls=9.4%<br>2-c) Mort. rate cases= 6.5%<br>Mort. rate controls=13% |                         |                          |                           |                                 |   |   |
| 9  | Manandhar 2016 <sup>219</sup> | 01/10-06/13 | Retrospective study        | a) Mort. rate cases= 26.7%<br>Mort. rate controls=38.1%<br>OR=0.62; 95%CI(0.15–2.61)<br>b) Mort. rate cases= 26.7%<br>Mort. rate controls=42.9%<br>OR=0.51; 95%CI(0.12–2.14)                            | Pittsburgh, USA         | a) 30 days<br>b) 90 days | 15 cases<br>21 controls   | bacteruria                      | no specific data                                      | all patients had S. aureus bacteruria also    |
| 10 | McMullan 2016 <sup>220</sup>  | 01/07-12/12 | Prospective cohort study   | a) Mort. rate cases= 3.5%<br>Mort. rate controls=2.5%<br>b) Mort. rate cases= 8.5%<br>Mort. rate controls=4.1%  | Australia & New Zealand | a) 7 days<br>b) 30 days  | 142 cases<br>931 controls | age                             | median (IQR)<br>cases=17 (8-38)<br>controls=14 (7-33) | patients were children                        |
| 11 | Nagao 2016 <sup>221</sup>     | 2006-2014   | Retrospective cohort study | Mort. rate cases= 9%<br>Mort. rate controls=5.8%  | Japan                   | 30 days                  | 199 cases<br>278 controls | BSI                             | no data   |   |
| 12 | Naidoo 2013 <sup>222</sup>    | 01/07-12/11 | Retrospective study        | MRSA OR (95%CI)<br>univariate=3.71 (1.77-7.76)*<br>multivariate=3.76 (1.12-12.67)*<br>*(p<0.05)   | South Africa            | 30 days                  | 95 cases<br>270 controls  | BSI                             | no specific data                                      | the mortality was not available in %          |
| 13 | Ong 2013 <sup>223</sup>       | 01/98-12/07 | Retrospective cohort study | Mort. rate cases= 63%<br>Mort. rate controls=39%<br>HR=1.37; 95%CI(0.95–1.97)   | Australia               | 1 year                   | 76 cases<br>363 controls  | none                            | no data   | the study aimed the long-term survival rate   |
| 14 | Park 2013 <sup>224</sup>      | 1998-2009   | Review and Meta-analysis   | OR fixed= 2.33; 95%CI(1.42-3.82)  | World                   | hospitaliz               | 191 cases<br>476 controls | age                             | no data   | all patients were neonates and children       |
| 15 | Simsek 2014 <sup>225</sup>    | 01/04-06/12 | Retrospective study        | Mort. rate cases= 49%<br>Mort. rate controls=15%<br>OR=12.117; 95%CI(3.159-46.475)  | Turkey                  | hospitaliz               | 13 cases<br>47 controls   | Poststernotomy<br>Mediastinitis | no specific data                                      | all patients had Poststernotomy Mediastinitis |



|    |                               |             |                               |   |                     |  |   |                  |                                 |  |
|----|-------------------------------|-------------|-------------------------------|---|---------------------|--|---|------------------|---------------------------------|--|
| 16 | Thaden 2015 <sup>226</sup>    | 1997-2012   | Retrospective study           | 1-a) Mort. rate cases= 3%<br>Mort. rate controls=4%<br>1-b) Mort. rate cases= 8%<br>Mort. rate controls=8%<br>1-c) Mort. rate cases= 11%<br>Mort. rate controls=10%<br>2-a) Mort. rate cases= 4%<br>Mort. rate controls=2%<br>2-b) Mort. rate cases= 9%<br>Mort. rate controls=3%<br>2-c) Mort. rate cases= 12%<br>Mort. rate controls=4% | North Carolina, USA | a) 7 days<br>b) 30 days<br>c) hospitaliz | 1) 567 cases<br>2047 controls<br>2) 280 cases<br>445 controls | age, ICU         | no data                         | all patients were infants in ICU<br>1) with adequate therapy<br>2) with inadequate therapy |
| 17 | Theodorou 2013 <sup>227</sup> | 01/89-12/09 | Retrospective cohort study    | Mort. rate cases= 33.3%<br>Mort. rate controls=24.4%<br>OR=1.55; 95%CI(0.56-4.28)   | Germany             | hospitaliz                               | 33 cases<br>41 controls                                       | thermal injuries | median cases=28.5<br>controls21 | all patients had thermal injuries  |
| 18 | Wang 2015 <sup>228</sup>      | 01/11-12/13 | Retrospective cohort study    | a) Mort. rate cases= 47.5%<br>OR=2.249; 95%CI(1.188-4.259)<br>b) Mort. rate cases= 30.5%<br>OR=0.998; 95%CI(0.453-2.200)<br>c) Mort. rate cases=35.3%<br>OR=1.223; 95%CI(0.466-3.210)<br>Mort. rate controls=25.3%<br>Total MRSA OR=1.707   | Taiwan              | hospitaliz                               | a) 101 cases<br>b) 59 cases<br>159 controls                   | none             | no data                         | a) HA-MRSA<br>b) CA-MRSA<br>c) unclassified-MRSA   |
| 19 | Yaw 2014 <sup>229</sup>       | 07/97-06/07 | Observational cohort study    | a) Mort. rate cases= 15%<br>Mort. rate controls=12%<br>b) Mort. rate cases= 28%<br>Mort. rate controls=19%<br>c) Mort. rate cases= 75%<br>Mort. rate controls=62%   | Australia           | a) 8 days<br>b) 30 days<br>c) follow-up* | 185 cases<br>397 controls                                     | none             | no data                         | * 01/03/2013   |
| 20 | Yilmaz 2016 <sup>230</sup>    | 2010-2012   | Prospective multicentre study | Mort. rate cases= 22%<br>Mort. rate controls=11.7%  | Turkey              | 28 days                                  | 100 cases<br>145 controls                                     | none             | no specific data                |  |

Table 46: Short extraction table of original articles on the mortality of MRSA bone infected patients vs MSSA skin wound infected patients

| Nr | Author                    | Study Period | Study type          | Outcome   | Location | Period of outcome | Population              | Matching criteria       | LOS (days) | Notes  |
|----|---------------------------|--------------|---------------------|---|----------|-------------------|-------------------------|-------------------------|------------|--|
| 1  | Shoji 2016 <sup>231</sup> | 01/07-12/11  | Retrospective study | Mort. rate cases= 25%<br>Mort. rate controls=5.5% | Japan    | hospitaliz        | 16 cases<br>55 controls | vertebral osteomyelitis | no data    | all patients had vertebral osteomyelitis infected by S. aureus |

Table 47: Short extraction table of original articles on the mortality of MRSA skin wound infected patients vs MSSA skin wound infected patients

| Nr | Author                       | Study Period | Study type            | Outcome                         | Location | Period of outcome | Population              | Matching criteria | LOS (days) | Notes |
|----|------------------------------|--------------|-----------------------|---------------------------------|----------|-------------------|-------------------------|-------------------|------------|-------|
| 1  | Alizadeh 2014 <sup>232</sup> | 2008-2010    | Cross-sectional study | No deaths reported in any group | Iran     | hospitaliz        | 82 cases<br>32 controls | none              | no data    |       |

Table 48: Short extraction table of original articles on mortality of patients with MRSA infections with mixed infection site vs non-infected patients

| Nr | Author                   | Study Period | Study type                 | Outcome   | Location  | Period of outcome         | Population                | Matching criteria | LOS (days) | Notes                                       |
|----|--------------------------|--------------|----------------------------|---|-----------|---------------------------|---------------------------|-------------------|------------|---|
| 1  | Balm 2013 <sup>233</sup> | 06/07-06/11  | Retrospective cohort study | a) Mort. rate cases= 16.5%<br>Mort. rate controls=4.6%<br>OR=5.49; 95%CI(2.75-10.95)<br>b) Mort. rate cases= 28.9%<br>Mort. rate controls=12.5% | Singapore | a) 30 days<br>b) 6 months | 121 cases<br>716 controls | none              | no data    | * controls had positive nasal swab for MRSA |

|   |                            |             |                            |   |           |            |  |                      |   |   |
|---|----------------------------|-------------|----------------------------|---|-----------|------------|--|----------------------|---|---|
|   |                            |             |                            | OR=2.94; 95%CI(1.78 – 4.85)   |           |            |  |                      |   |   |
| 2 | Nelson 2015 <sup>234</sup> | 10/07-09/10 | Retrospective cohort study | a) MRSA aHR (95%CI)=1.420(1.322-1.525)*<br>b) MRSA aHR (95%CI)=1.370(1.231-1.524)*<br>*(p<0.05)         | Utah, USA | 1 year     | a) 3599 cases<br>366144 controls<br>b) 3592 cases<br>3592 controls | propensity score (b) | mean<br>a) cases=22.4<br>controls=9.3<br>b) cases=20.1<br>controls=23.2 | a) full cohort<br>b) propensity score matched |
| 3 | Tran 2016 <sup>235</sup>   | 01/10-12/12 | Retrospective cohort study | a)Mort. rate cases=8.2%<br>Mort. rate controls=5.7%<br>b)Mort. rate cases= 8%<br>Mort. rate controls=7% | Canada    | hospitaliz | 745 cases<br>17649 cosntrols                                       | none                 | mean<br>a)cases=12.8<br>controls=7.6<br>b) cases=11.9<br>controls=9.1   | a) pre-match cohort<br>b) post-match cohort   |

Table 49: Short extraction table of original articles on mortality of patients with MRSA infections with mixed infection site vs patients with MSSA infections

| <b>N r</b> | <b>Author</b>               | <b>Study Period</b> | <b>Study type</b>               | <b>Outcome</b>   | <b>Location</b> | <b>Period of outcome</b>                      | <b>Population</b>           | <b>Matching criteria</b> | <b>LOS (days)</b>                                 | <b>Notes</b>             |
|------------|-----------------------------|---------------------|---------------------------------|--|-----------------|---|-----------------------------|--------------------------|---|--------------------------|
| 1          | Ericson 2015 <sup>236</sup> | 1997-2012           | Multicentre retrospective study | a)Mort. rate cases= 11.9%<br>Mort. rate controls=9.6%<br>RR=1.19; 95%CI(0.96-1.49)<br>b)Mort. rate cases= 3.8%<br>Mort. rate controls=3.8%<br>RR=0.90; 95%CI(0.65-1.24)<br>c)Mort. rate cases= 8.7%<br>Mort. rate controls=7.2%<br>RR=1.15; 95%CI(0.90-1.46) | USA             | a) before discharge<br>b) 7days<br>c) 30 days | 1063 cases<br>2825 controls | NICU                     | Both groups=64                                    | Patients were in NICU    |
| 2          | Gimenes 2016 <sup>237</sup> | 2006-2011           | Retrospective study             | Mort. rate cases= 33.8%<br>Mort. rate controls=52.17%  | Brazil          | hospitaliz                                    | 71 cases<br>23 controls     | ICU                      | median (IQR)<br>cases=20 (20)<br>controls=19 (17) | all patients were in ICU |

|   |                                |                 |                      |  |                |         |                           |      |         |                                      |
|---|--------------------------------|-----------------|----------------------|--|----------------|---------|---------------------------|------|---------|--------------------------------------|
| 3 | Kim E.S<br>2014 <sup>238</sup> | 01/12-<br>12/12 | Prospective<br>study | Mort. rate cases= 16.8%<br>Mort. rate controls=14% | South<br>Korea | 30 days | 303 cases<br>357 controls | none | no data | the infection had<br>community onset |
|---|--------------------------------|-----------------|----------------------|--|----------------|---------|---------------------------|------|---------|--------------------------------------|

Table 50: Short extraction table of original articles on mortality of patients colonised with MRSA in the nasal mucosa vs no-colonised patients

| N<br>r | Author                          | Study<br>Period | Study type                    | Outcome   | Location      | Period of<br>outcome | Population               | Matching criteria  | LOS (days)                                       | Notes  |
|--------|---------------------------------|-----------------|-------------------------------|---|---------------|----------------------|--------------------------|--|--|--|
| 1      | Altinbas<br>2013 <sup>239</sup> | 04/06-<br>04/07 | Prospective<br>study          | Mort. rate cases= 18.1%<br>Mort. rate controls=37.3%  | Turkey        | 1 year               | 11 cases<br>257 controls | ICU  | mean<br>cases=18<br>controls=8                   | the difference in<br>mortality is not<br>statistically significant   |
| 2      | Chan<br>2015 <sup>240</sup>     | 11/08-<br>12/09 | Prospective<br>cohort study   | a) Mort. rate cases= 64%<br>Mort. rate controls=44.6%<br>b) Mort. rate cases= 30.7%<br>Mort. rate controls=18.8%<br>HR=1.96, 95%CI(1.01-3.78) | Hong<br>Kong  | hospitaliz           | 75 cases<br>117 controls | none   | all patients<br>were in a<br>nursing<br>home     | a) all-cause mortality<br>b) infection related<br>mortality*<br>* according to<br>International<br>Classification of<br>Diseases, 9th Revision,<br>Clinical Modification |
| 3      | Chen<br>2013 <sup>241</sup>     | 07/09-<br>06/10 | Retrospective<br>cohort study | Mort. rate cases= 12.2%<br>Mort. rate controls=15.6%  | Texas,<br>USA | hospitaliz           | 90 cases<br>90 controls  | none   | mean±SD<br>cases=5.2±7.4<br>controls=5.9±<br>8.8 |  |
| 4      | Moore<br>2014 <sup>242</sup>    | 01/07-<br>12/12 | Retrospective<br>study        | a) Mort. rate cases= 17%<br>Mort. rate controls=7%<br>b) Mort. rate cases= 3.6%<br>Mort. rate controls=0%                                     | Ireland       | 5 years              | 28 cases<br>56 controls  | age & gender<br>recipient &<br>donor, CMI, cause<br>of renal failure<br>pre-operatively,<br>date of transpl. | no data  | all patients were renal<br>transplant recipients<br>a) all-cause mortality<br>b) infection related<br>mortality  |

Table 51: Short extraction table of original articles on respiratory tract infections mortality of MRSA infected patients vs non-infected patients

| Nr | Author                       | Study Period | Study type          | Outcome   | Location        | Period of outcome | Population                | Matching criteria | LOS (days)                  | Notes                             |
|----|------------------------------|--------------|---------------------|---|-----------------|-------------------|---------------------------|-------------------|-----------------------------|-----------------------------------|
| 1  | Minejima 2014 <sup>243</sup> | 01/05-10-11  | Retrospective study | Mort. rate cases= 22%<br>Mort. rate controls=3% | California, USA | 28 days           | 134 cases<br>134 controls | pneumonia         | mean cases=10<br>controls=5 | * patients had non-MRSA pneumonia |

Table 52: Short extraction table of original articles on respiratory tract infections mortality of MRSA infected patients vs MSSA infected patients

| Nr | Author                    | Study Period | Study type                            | Outcome  | Location                 | Period of outcome | Population   | Matching criteria | LOS (days)  | Notes  |
|----|---------------------------|--------------|---------------------------------------|--|--------------------------|-------------------|--|-------------------|---|--|
| 1  | Hill 2013 <sup>244</sup>  | 01/04-12/09  | Retrospective study                   | Mort. rate cases= 17.5%<br>Mort. rate controls=25.4%   | Tennessee, USA           | hospitaliz        | no exact data*<br>~80 cases<br>~60 controls            | VAP               | in ICU<br>mean cases=34<br>controls=35                | patients had Ventilator-associated pneumonia (VAP)<br>*population estimated from graph   |
| 2  | Tosh <sup>245</sup> 2013  | 09/08-08/10  | Retrospective study                   | Mort. rate cases= 12%<br>Mort. rate controls=2%  | USA                      | hospitaliz        | 42 cases<br>52 controls                                | LRI               | mean cases=9<br>controls=6                            | all patients had lower respiratory tract infection (LRI)   |
| 3  | Jung 2013 <sup>246</sup>  | 01/08-12/11  | Retrospective study                   | Mort. rate cases= 33.3%<br>Mort. rate controls=21.5%   | South Korea              | hospitaliz        | 78 cases<br>865 controls*                              | pneumonia         | median (IQR) cases=16.5 (10-30)<br>controls=11 (6-20) | * controls were patients with non-nosocomial pneumonia due to other bacteria (non-MRSA)  |
| 4  | Rello 2013 <sup>196</sup> | not clear    | Retrospective comparison of 2 cohorts | a) Mort. rate cases= 33.3%<br>Mort. rate controls=10%<br>b) Mort. rate cases= 60%<br>Mort. rate controls=50% | Europe & Latin America * | in ICU            | a) 15 cases<br>30 controls<br>b) 5 cases<br>6 controls | none              | no data   | all patients had pneumonia and were in ICU<br>*the study aimed to compare 2 cohorts from different continents<br>a) Europe<br>b) Latin America |
| 5  | Self 2016 <sup>247</sup>  | 2,5 years    | Prospective study                     | Mort. rate cases= 13.3%<br>Mort. rate controls=9.1%  | Australia                | hospitaliz        | 15 cases<br>22 controls                                | CA-pneumonia      | median (IQR) cases=9 (8-                              | all patients had CA-pneumonia  |

|  |  |  |  |  |  |  |  |  |                             |  |
|--|--|--|--|--|--|--|--|--|-----------------------------|--|
|  |  |  |  |  |  |  |  |  | 13)<br>controls=6<br>(4-10) |  |
|--|--|--|--|--|--|--|--|--|-----------------------------|--|

Table 53: Short extraction table of original articles on joint infections mortality of MRSA infected patients vs MSSA infected patients

| Nr | Author                      | Study Period | Study type           | Outcome  | Location | Period of outcome | Population              | Matching criteria | LOS (days)                   | Notes   |
|----|-----------------------------|--------------|----------------------|--|----------|-------------------|-------------------------|-------------------|------------------------------|---|
| 1  | Lin 2015 <sup>248</sup>     | 01/08-12/11  | Clinical case-series | Mort. rate cases= 5.3%<br>Mort. rate controls=5.5%   | Taiwan   | hospitaliz        | 38 cases<br>55 controls | joint infection   | no data                      | all patients had septic arthritis caused by S. aureus |
| 2  | Minguez 2015 <sup>249</sup> | 1984-2011    | Retrospective study  | Mort. rate cases= 57.1%<br>Mort. rate controls=17.6% | Mexico   | hospitaliz        | 7 cases<br>17 controls  | joint infection   | mean cases=33<br>controls=20 | all patients had septic arthritis due to S. aureus    |

During the review we have identified an article of 2011(Lambert et al.<sup>50</sup>) which was not included in WHO review and which reports mortality data for MRSA and MSSA patients with BSI and pneumonia. We decided to report the results of this article given its high quality.

Table 54: Short extraction table of the original article reporting BSI and pneumonia infections due to MRSA vs MSSA organisms.

| Nr | Author                     | Study Period | Study type               | Outcome  | Location | Period of outcome   | Population  | Matching criteria | LOS (days)  | Notes  |
|----|----------------------------|--------------|--------------------------|--|----------|---------------------|---|-------------------|---|--|
| 1  | Lambert 2011 <sup>50</sup> | 01/05-12/08  | Prospective cohort study | a) Mort. cases=38%<br>Mort. controls=26%<br>aHR=1.6; 95%CI(1.1-2.3)<br>b) Mort. cases=33%<br>Mort. controls=23%<br>aHR=1.3; 95%CI(1.0-1.6) | Europe   | ICU hospitalization | a)171 cases<br>284 controls<br>b)524 cases<br>1014 controls | ICU               | From infection to discharge median (IQR)<br>a)cases=14(6-24)<br>controls=11 (5-24)<br>b)cases= 15(8-27)<br>controls=14 (8-25) | patients were in ICU<br>a)patients with BSI<br>b)patients with pneumonia |

Additionally to the primary studies included in the WHO AMR report and in our literature review, we would like to report the analytical study from de Kraker et al of 2011<sup>250</sup>. In this study the authors estimate the excess number of deaths, bed-days and hospital costs associated with BSI caused by MRSA and G3CREC in 31 European countries that participated in the EARSS for 2007. Official data from ECDC, WHO and OECD together with previously published mortality data<sup>61,193</sup> and model equations<sup>251</sup> are used to model the indicators for each country individually and for all of them pooled. The results resumed are: "In 2007, 27,711 episodes of MRSA BSIs were associated with 5,503 excess deaths and 255,683 excess hospital days in the participating countries, whereas 15,183 episodes of G3CREC BSIs were associated with 2,712 excess deaths and 120,065 extra hospital days. The total costs attributable to excess hospital stay were 44.0 and 18.1 million euros (63.1 and 29.7 million international dollars), respectively." For further details on the methodology and country specific results we invite the reader to access the full text article.

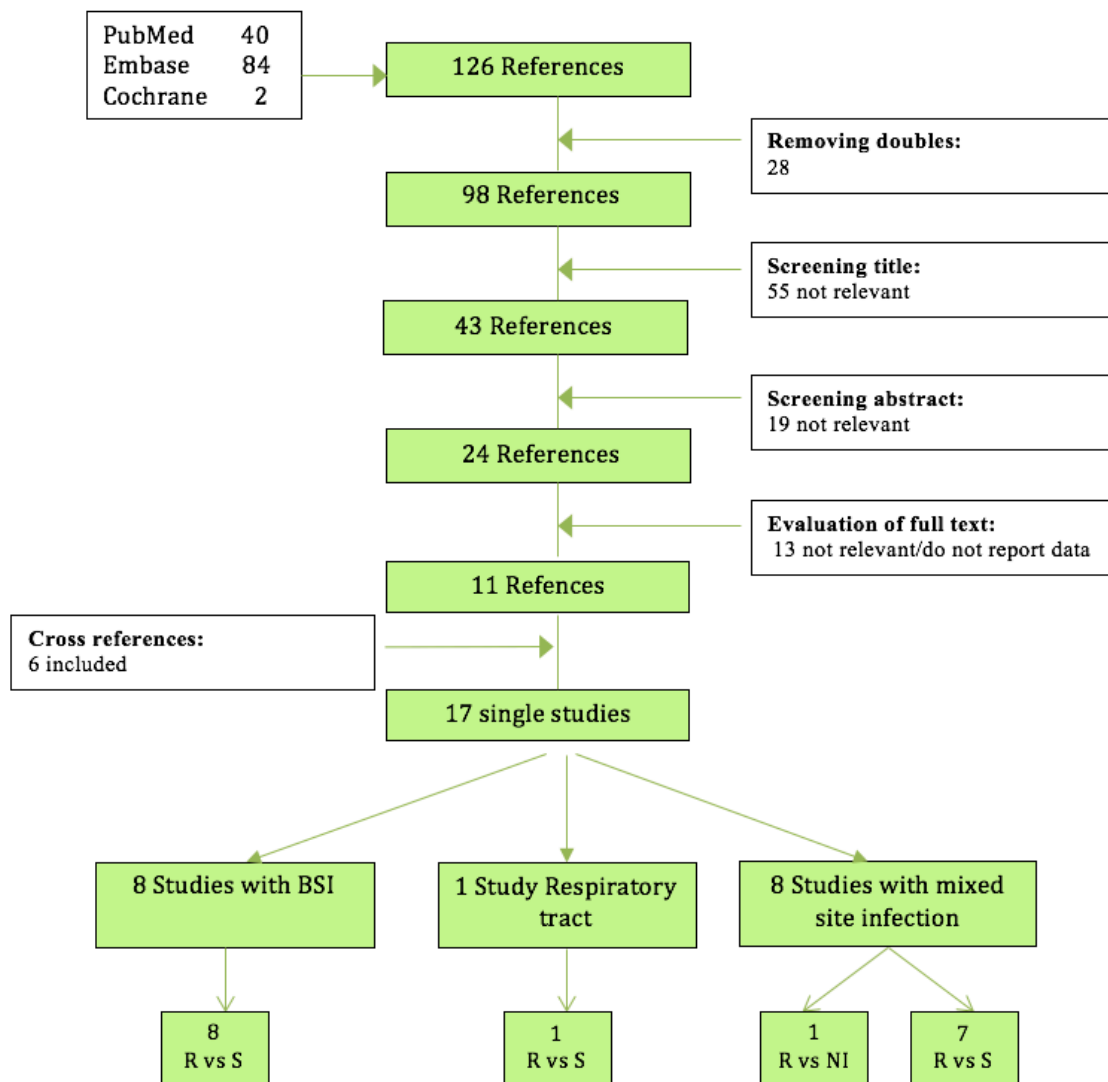
## 11. Carbapenem resistant *Pseudomonas aeruginosa*

To research the attributable case fatality and the attributable LOS to carbapenem resistant *Pseudomonas aeruginosa* (CRPA) we performed 2 advanced searches on Pubmed using once the mesh term "Pseudomonas aeruginosa" AND all fields "carbapenem resistant" AND "mortality", and the second time the mesh term "Pseudomonas aeruginosa" AND all fields "carbapenem resistance" AND "mortality". Embase was searched for 'Pseudomonas aeruginosa' AND 'carbapenem resistant' AND 'mortality', and 'Pseudomonas aeruginosa AND 'carbapenem resistance' AND 'mortality'. We applied a filter to include only human studies. An advanced search on the Cochrane Library was performed using terms "Pseudomonas aeruginosa" AND "carbapenem". No language restrictions were made, and no further filters were applied.

The flow diagram, presented in Figure 11 describes the steps in the literature review of carbapenem resistant *Pseudomonas aeruginosa* infections. The results obtained using the two different strings for PubMed and Embase were aggregated.

Once identified the studies reporting relevant data, these were grouped based on the site of infection.

Figure 11: Search for studies on carbapenem resistant *Pseudomonas aeruginosa*. Inclusion and exclusion diagram.



As shown in Figure 11, 6 studies were not detected by our searching strategy (because they used imipenem in their key words instead of the generic term carbapenem) and included in the review because were found in a meta-analysis from Liu et al, 2015<sup>252</sup> which was part of our results.

The following tables include studies reporting results for BSI, respiratory tract and for mixed site of infection due to CRPA, based on the comparison group they used. All information is reported as was presented in the original papers.

Studies that include both a sensitive and a non-infected control group, were categorised in the latter group.



Table 55: Short extraction table of original articles on BSI mortality of CRPA infected patients vs CSPA infected patients

| Nr | Author                       | Study Period | Study type                    | Outcome   | Location      | Period of outcome    | Population                | Matching criteria | LOS (days)  | Notes   |
|----|------------------------------|--------------|-------------------------------|---|---------------|----------------------|---------------------------|-------------------|---|---|
| 1  | Dantas 2014 <sup>253</sup>   | 05/09-08/11  | Retrospective study           | Mort. cases= 47.3%<br>Mort. controls= 36.9%<br>OR=1.53  | Brazil        | 30 days              | 55 cases<br>65 controls   | BSI               | mean (range)<br>cases=48(4-205)<br>controls=41(3-378) |   |
| 2  | Hattemer 2013 <sup>254</sup> | 08/99-01/10  | Retrospective study           | Mort. cases= 54%<br>Mort. controls= 32%   | New York, USA | 30 days              | 13 cases<br>137 controls  | BSI               | no data   | patients had HAI or CAI   |
| 3  | Joo 2011 <sup>255</sup>      | 10/07-03/09  | Retrospective cohort study    | Mort. cases= 39.1%<br>Mort. controls= 21.2%<br>OR=2.40; 95%CI(1.18–4.86)<br>aOR=2.74; 95%(1.02–7.37)* | Korea         | 30 days              | 46 cases<br>156 controls  | BSI               | median (IQR)<br>cases=16(14-42)<br>controls=16(9-29)  | *adjusted for corticosteroid use, nosocomial acquisition, polymicrobial infection, Charlson's weighted index of co-morbidity, and admission to ICUs |
| 4  | Kang 2005 <sup>256</sup>     | 01/98-12/02  | Retrospective study           | Mort. cases= 53.6%<br>Mort. controls= 35.2%<br>OR=2.216; 95%CI(0.946–4.776)                           | Korea         | 30 days              | 28 cases<br>158 controls  | none              | no data   |   |
| 5  | Kim 2014 <sup>257</sup>      | 01/10-12/12  | Retrospective study           | Mort. cases= 22.0%<br>Mort. controls= 22.4%<br>OR=3.65; 95%CI(0.72-18.67)                             | Korea         | 14 days              | 118 cases<br>116 controls | BSI               | no data   | the study was focused on survivors and non-survivors  |
| 6  | Pena 2012 <sup>258</sup>     | 01/08-12/09  | Prospective multicentre study | a) Mort. cases= 13%<br>Mort. controls= 13%<br>b)Mort. cases= 35%<br>Mort. controls= 27%               | Spain         | a) 48h<br>b) 30 days | 145 cases<br>487 controls | BSI               | no data   |   |
| 7  | Suarez 2010 <sup>259</sup>   | 01/05-12/05  | Retrospective cohort study    | Mort. cases= 46%<br>Mort. controls= 36%<br>*Attribut. mort. cases=33%<br>Attribut. mort. controls=30% | Spain         | 30 days              | 33 cases<br>88 controls   | BSI               | mean (range)<br>cases=19(2-98)<br>controls=9(2-56)    | *within 7 days from BSI and excluding other causes  |

|   |                          |             |                    |  |        |         |                         |     |  |  |
|---|--------------------------|-------------|--------------------|--|--------|---------|-------------------------|-----|--|--|
|   |                          |             |                    | OR=1.8; 95%CI(0.5–6.8)   |        |         |                         |     |  |  |
| 8 | Tuon 2012 <sup>260</sup> | 01/06-01/09 | Case-control study | Mort. cases= 54.2%<br>Mort. controls= 44.8%<br>OR=0.68; 95%CI(0.27–1.73) | Brazil | 30 days | 29 cases<br>48 controls | BSI | mean±SD<br>cases=43±31.7<br>controls=43.1±31.2 |  |

Table 56: Short extraction table of original articles on respiratory tract infection mortality of CRPA infected patients vs CSPA infected patients

| Nr | Author                   | Study Period | Study type                      | Outcome                                 | Location | Period of outcome | Population                | Matching criteria | LOS (days)  | Notes   |
|----|--------------------------|--------------|---------------------------------|---|----------|-------------------|---------------------------|-------------------|---|---|
| 1  | Luyt 2014 <sup>261</sup> | 18 months    | Prospective observational study | Mort. cases= 37%<br>Mort. controls= 31% | France   | In ICU stay       | 68* cases<br>101 controls | none              | median (IQR)<br>cases=37(23-57)<br>controls=29(19-46) | * cases included resistant and intermediate susceptible PA, was not possible to separate them |

Table 57 and Table 58 present the results of studies that include patients with different sites of infection. Almost all the articles specify the number of cases for the different infection sites but they do not report different mortalities based on the infection site. When it was possible the results are presented differentiating the mortality for each site of infection. The study in Table 57 includes a not infected and a susceptible infected control group.

Table 57: Short extraction table of original articles on mortality of CRKP infected vs non infected vs CSPA infected patients, for different infection sites

| Nr | Author                    | Study Period | Study type                 | Outcome  | Location         | Period of outcome | Population                                       | Matching criteria | LOS (days)   | Notes |
|----|---------------------------|--------------|----------------------------|--|------------------|-------------------|--|-------------------|--|-------|
| 1  | Eagye 2009 <sup>262</sup> | 02/06-10/06  | Case-control-control study | Mort. resist= 31%<br>Mort. sensit= 15%<br>Mort. control=9% | Connecticut, USA | hospitaliz        | 58 resistant<br>125 sensitive<br>57 non infected | none              | median(IQR)<br>resist=30(15-70)<br>sensit=16(6-33)<br>control=10(6-17) |       |

Table 58: Short extraction table of original articles on mortality of CRPA infected patients vs CSPA infected patients for different infection sites

| Nr | Author  | Study Period | Study type                               | Outcome   | Location         | Period of outcome | Population                 | Matching criteria  | LOS (days)  | Notes   |
|----|---|--------------|--|---|------------------|-------------------|----------------------------|--|---|---|
| 1  | Judd 2016 <sup>263</sup>                                      | 01/11-12/13  | Retrospective observational cohort study | Mort. cases= 28.1%<br>Mort. controls= 8.9%<br>OR=2.89; 95%CI(1.15-7.28)       | Kentucky, USA    | hospitaliz        | 32 cases<br>350 controls   | none   | median (IQR)<br>cases=14(8-29)<br>controls=9(5-15)  |   |
| 2  | Lautenbach 2006 <sup>264</sup>                                | 01/91-12/00  | Case-control study                       | Mort. cases= 31.1%<br>Mort. controls= 16.7%<br>RR=1.86; 95%CI(1.38-2.51)      | Pennsylvania USA | hospitaliz        | 142 cases<br>737 controls  | none   | median (IQR)<br>cases=11(1-41)<br>controls=4(1-15)  | study considers all the cases recovered with PA |
| 3  | Lautenbach 2010 <sup>265</sup>                                | 01/01-12/06  | Case-control study                       | Mort. cases= 17.4%<br>Mort. controls= 13.4%<br>RR=1.39; 95%CI(1.09-1.76)      | Pennsylvania USA | hospitaliz        | 253 cases<br>2289 controls | none   | prior isolation<br>median (IQR)<br>cases=8(4-12)<br>controls=4(4-5)                             | study considers all the cases recovered with PA |
| 4  | Lin 2014 <sup>266</sup>                                       | 01/00-12/10  | Retrospective study                      | Mort. cases= 22.0%<br>Mort. controls= 19.5%                                   | Taiwan           | hospitaliz        | 82 cases<br>82 controls    | none   | no data   | matched randomly by computer                    |
| 5  | Liu 2015 <sup>252</sup>                                       | 1994-2014    | Meta-analyses                            | Crude OR=1.64<br>(95%CI=1.40, 1.93)<br>Adjusted OR=2.38<br>(95%CI=1.53, 3.69) | World            |                   | 16 studies                 |  |   |   |
| 6  | Meradji 2015 <sup>267</sup>                                   | 01/12-12/13  | Prospective observational study          | Mort. cases= 13.34%<br>Mort. controls= 1.53%                                  | Morocco          | hospitaliz        | 15 cases<br>65 controls    | none   | no data   |   |
| 7  | Brooklyn Antibiotic Resistance Task Force 2002 <sup>268</sup> | 1999         | Matched case-control study               | Mort. cases= 20%<br>Mort. controls= 10%                                       | USA              | hospitaliz        | 10 cases<br>10 controls    | age, site of infection, major diagnosis, operative procedures, type of infection | median<br>preinfection<br>cases=12<br>controls=15<br>postinfection<br>cases=33.5<br>controls=20 |   |

Many studies were excluded because they did not report a comparison group. Other studies identified were genetic analyses and were not eligible for the purposes of this review.

We also identified a meta-analysis that calculated the mortality due to carbapenem resistant *Pseudomonas aeruginosa* compared to a susceptible group. The published studies included in this meta-analysis were also identified in our literature search, except for six publications which we subsequently included since they fulfilled the eligibility criteria.

We decided to report in this chapter the study of Lambert et al<sup>50</sup> since it included information on 3<sup>rd</sup> generation cephalosporin resistant *Pseudomonas aeruginosa*, which might be useful in the evaluation of the resistances of this bacterium. This article studied the mortality rates of patients with BSI or pneumonia due to 3<sup>rd</sup> generation cephalosporin resistant *P. aeruginosa* (3GCRPA) and 3<sup>rd</sup> generation cephalosporin susceptible *P. aeruginosa* (3GCSPA)

Table 59: Short extraction table of the original article reporting BSI and pneumonia infections due to 3GCRPA vs 3GCSPA organisms

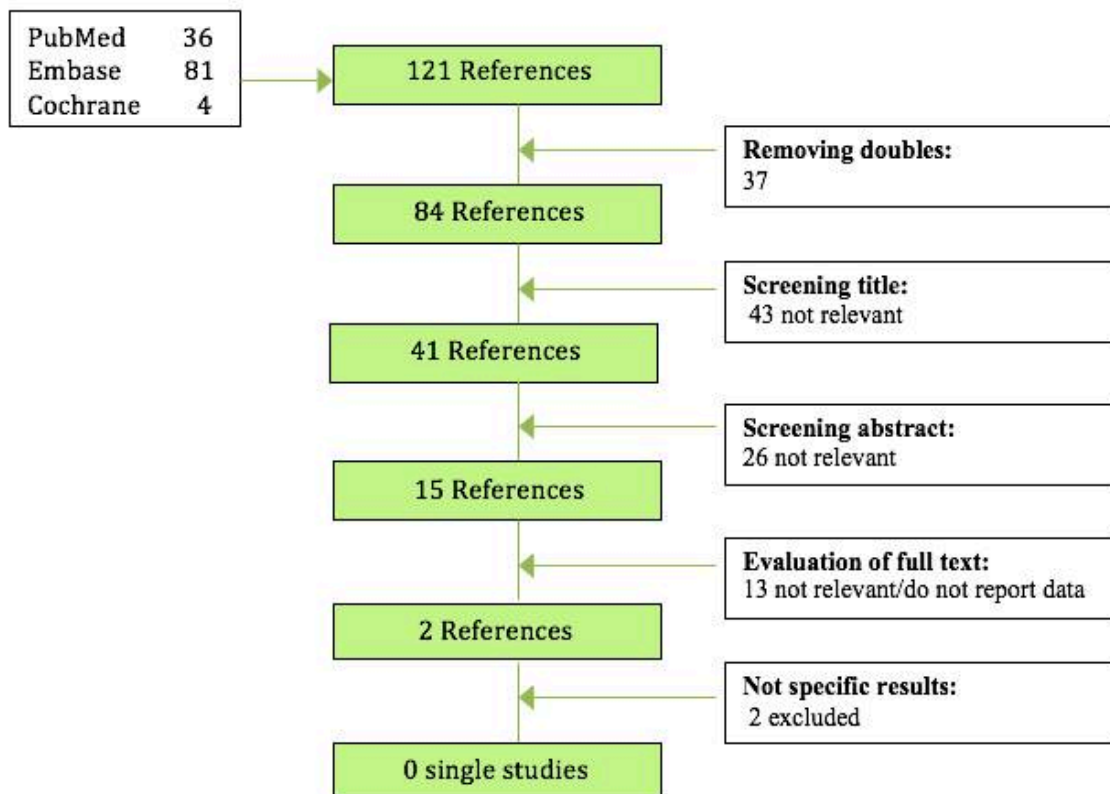
| Nr | Author                     | Study Period | Study type               | Outcome  | Location | Period of outcome   | Population   | Matching criteria | LOS (days)   | Notes  |
|----|----------------------------|--------------|--------------------------|--|----------|---------------------|--|-------------------|--|--|
| 1  | Lambert 2011 <sup>50</sup> | 01/05-12/08  | Prospective cohort study | a) Mort. cases=41%<br>Mort. controls=39%<br>aHR=1.2; 95%CI(0.8-1.9)<br>b) Mort. cases=43%<br>Mort. controls=37%<br>aHR=1.2; 95%CI(1.0-1.5) | Europe   | ICU hospitalization | a)82 cases<br>282 controls<br>b)366 cases<br>1266 controls | ICU               | From infection to discharge median (IQR)<br>a)cases=16(7-33)<br>controls=14 (6-26)<br>b)cases= 18(11-33)<br>controls=16 (9–29) | patients were in ICU<br>a)patients with BSI<br>b)patients with pneumonia |

## 12. Colistin resistant *Pseudomonas aeruginosa*

To research the attributable case fatality and the attributable LOS to colistin resistant *Pseudomonas aeruginosa* (CoRPA) we performed 2 advanced searches on Pubmed using once the mesh term “*Pseudomonas aeruginosa*” AND all fields “colistin resistant”, and the second time the mesh term “*Pseudomonas aeruginosa*” AND all fields “colistin resistance”. Embase was searched for ‘*Pseudomonas aeruginosa*’ AND ‘colistin resistance’, and for ‘*Pseudomonas aeruginosa*’ AND ‘colistin resistant’. In Embase studies was filtered, including just those conducted in humans. An advanced search on the Cochrane Library was performed using terms “*Pseudomonas aeruginosa*” AND “colistin”. No language restrictions were made, and no other filters were applied.

The flow diagram, presented in Figure 12 describes the steps in the literature review of colistin resistant *Pseudomonas aeruginosa* infections. The results obtained using the two different key words in PubMed and Embase were aggregated.

Figure 12: Search for studies on colistin resistant *Pseudomonas aeruginosa*. Inclusion and exclusion diagram.



The review did not identify any published study eligible with the selection criteria. However, two articles reported studies on colistin resistance in patients infected with *Pseudomonas aeruginosa*.

Matthaiou et al. in 2008<sup>269</sup> studied the risk factors associated with the isolation of colistin-resistant Gram-negative bacteria in a matched case-control study. Amongst 40 patients, two reported a CoRPA infection but the sample could not be considered representative. Yilmaz et al 2016<sup>270</sup>, also studied the risk factors of colistin-resistant Gram-negative bacteria in a multicentre study and included in their sample of 56 resistant patients, 18 infected with CoRPA. The sample is more representative but the results of the study are presented pooled together for all patients infected with Gram-negative bacteria. They reported a mortality rate of cases (resistant to colistin) of 53.6%, compared to the mortality rate of controls (sensitive to colistin) of 45%.

The colistin resistant *Pseudomonas aeruginosa* infections are a relatively new research topic, and it seems that no structured studies were conducted yet to investigate the burden of these infections in terms of attributable mortality or attributable length of stay in hospital.

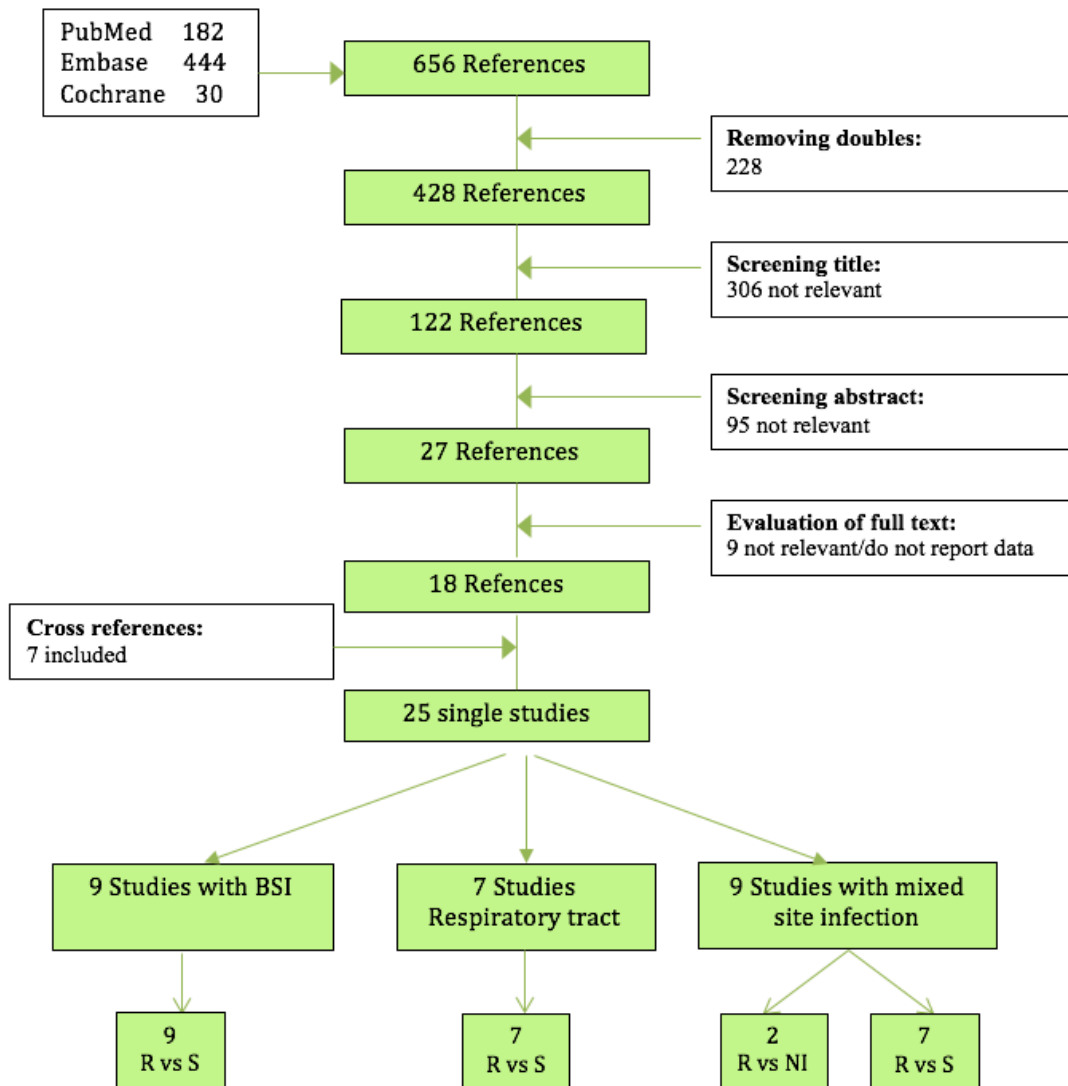
### 13. Multidrug resistant *Pseudomonas aeruginosa*

For the purposes of these project a multidrug resistant isolate is defined as resistant to at least three classes of antimicrobial agents, all penicillins and cephalosporins (including inhibitor combinations), fluroquinolones, and aminoglycosides. Here are excluded those resistant to carbapenem and/or to colistin. If an isolate is multidrug resistant and also resistant to carbapenem and/or colistin, it will be classified as resistant to the latter antibiotic.

To research the attributable case fatality and the attributable LOS to multidrug resistant *Pseudomonas aeruginosa* (MDRPA) we performed 3 advanced searches on Pubmed using once the mesh term “*Pseudomonas aeruginosa*” AND all fields “multidrug resistant” AND all fields “mortality”, the second time the mesh term “*Pseudomonas aeruginosa*” AND all fields “multidrug resistance” AND all fields “mortality”, and the third time the mesh term “*Pseudomonas aeruginosa*” AND all fields “MDR” AND all fields “mortality”. A filter for human studies was applied. Embase was also searched for 3 different strings; once ‘*Pseudomonas aeruginosa*’ AND ‘multidrug resistant’ AND ‘mortality’, the second time ‘*Pseudomonas aeruginosa*’ AND ‘multidrug resistance’ AND ‘mortality’, and the third time ‘*Pseudomonas aeruginosa*’ AND ‘MDR’ AND ‘mortality’. We applied a filter to include only human studies. Two advanced searches were also performed on the Cochrane Library using once the terms “*Pseudomonas aeruginosa*” AND “multidrug resistant”, and the second time the terms “*Pseudomonas aeruginosa*” AND “multidrug resistance”. No language restrictions were made, and no further filters were applied.

The flow diagram, presented in Figure 13 describes the steps in the literature review of multidrug resistant *Pseudomonas aeruginosa* infections. The results obtained using the different strings for PubMed, Embase and the Cochrane Library were summed up together.

Figure 13: Search for studies on multidrug resistant *Pseudomonas aeruginosa*. Inclusion and exclusion diagram.



The following tables include studies reporting results for BSI, respiratory tract and for mixed site of infection due to MDRPA, based on the comparison group they used. All information is reported as was presented in the original papers.



Table 60: Short extraction table of original articles on BSI mortality of MDRPA infected patients vs MDSPA infected patients

| Nr | Author                         | Study Period | Study type                 | Outcome  | Location     | Period of outcome  | Population                | Matching criteria    | LOS (days)  | Notes  |
|----|--------------------------------|--------------|----------------------------|--|--------------|--|---------------------------|----------------------|---|--|
| 1  | Caselli 2010 <sup>271</sup>    | 01/00-12/08  | Retrospective study        | Mort. rate cases=35%.8<br>Mort. rate controls=12.5%<br>aOR=4.3; 95%CI(1.67-11.07)  | Italy        | 30 days  | 39 cases<br>88 controls   | underlying condition | no data   | patients were children under chemotherapy and HSC transplant |
| 2  | Johnson 2009 <sup>272</sup>    | 01/96-12/05  | Retrospective cohort study | Mort. rate cases=36.6%<br>Mort. rate controls=46%<br>OR=0.68; 95%CI(0.27-1.71)   | Boston, USA  | 28 days  | 41 cases<br>50 controls   | transplant           | no specific data  | patients were trasplant recipients                           |
| 3  | Morata 2012 <sup>273</sup>     | 01/00-12/08  | Prospective study          | Mort. rate cases=17.2%<br>Mort. rate controls=32.3%  | Spain        | 30 days  | 127 cases<br>582 controls | BSI                  | mean±SD<br>cases=31.83±30<br>controls=16.38±18                      |  |
| 4  | Tam 2010 <sup>274</sup>        | 01/05-12/08  | Retrospective cohort study | I) Mort. rate cases=40%<br>Mort. rate controls=11.9%<br>OR=6.829; 95%CI(1.945–23.984)<br>II) Mort. rate cases=52%<br>Mort. rate controls=9.5%<br>III) Mort. rate cases=56%<br>Mort. rate controls=16.7%<br>IV) c) Mort. rate cases=61.9%<br>Mort. rate controls=9.5% | Houston, USA | I) 30 days<br>II) infection related<br>III) overall mortality<br>IV) matched pairs | 25 cases<br>84 controls   | BSI                  | prior isolation<br>mean±SD<br>cases=32.6±37.3<br>controls=14.4±43.6 |  |
| 5  | Theodorou 2013 <sup>275</sup>  | 01/89-12/09  | Retrospective cohort study | Mort. rate cases=42.2%<br>Mort. rate controls=45.2%<br>OR=1.076; 95%CI(0.356–3.254)  | Germany      | hospitaliz   | 45 cases<br>42 controls   | underlying condition | prior isolation<br>mean±SD<br>cases=28.2±23.8<br>controls=26.6±22.3 | patients were in a burn ICU                                  |
| 6  | Trecarichi 2011 <sup>276</sup> | 01/09-?      | Prospective study          | Mort. rate cases=40.7%<br>Mort. rate controls=9.1%   | Italy        | 21 days  | 27 cases<br>11 controls   | underlying condition |   | patients had haematological malignancies                     |

|   |                                |             |                            |  |        |         |                          |     |   |   |
|---|--------------------------------|-------------|----------------------------|--|--------|---------|--------------------------|-----|---|---|
| 7 | Tumbarello 2011 <sup>277</sup> | 01/06-12/07 | Case-case-control study    | Mort. rate cases=50%<br>Mort. rate controls=24.2%  | Italy  | 21 days | 40 cases<br>66 controls  | BSI | mean±SD<br>cases=27±14<br>controls=17±13                |   |
| 8 | Dantas 2014 <sup>253</sup>     | 05/09-08/11 | Retrospective study        | Mort. rate cases=42.1%<br>Mort. rate controls=41.2%  | Brazil | 30 days | 57 cases<br>63 controls  | BSI | mean (range)<br>cases=59 (4–205)<br>controls=62 (3–378) |   |
| 9 | Joo 2011 <sup>255</sup>        | 10/07-03/09 | Retrospective cohort study | Mort. rate cases=38.1%<br>Mort. rate controls=21.9%<br>OR=2.20; 95%CI(1.06–4.55)<br>aOR=2.24; 95%CI (0.80–6.29)* | Korea  | 30 days | 42 cases<br>160 controls | BSI | median (IQR)<br>cases=25 (13–38)<br>controls=16 (10–31) | *adjusted for corticosteroid use, nosocomial acquisition, polymicrobial infection, Charlson's weighted index of co-morbidity, and admission to ICUs |

Table 61: Short extraction table of original articles on respiratory tract infection mortality of MDRPA infected patients vs MDSPA infected patients

| Nr | Author                       | Study Period | Study type                      | Outcome  | Location | Period of outcome | Population                | Matching criteria                                   | LOS (days)  | Notes  |
|----|------------------------------|--------------|---------------------------------|--|----------|-------------------|---------------------------|---|---|--|
| 1  | Cilloniz 2016 <sup>278</sup> | 01/99-12/14  | Prospective observational study | Mort. Rate cases=22.7%<br>Mort. rate controls=17.4%                        | Spain    | 30 days           | 22 cases<br>46 controls   | pneumonia   | median (IQR)<br>cases=14(12-21)<br>controls=11(7-16)    | patients had all CAI                                 |
| 2  | Montero 2009 <sup>279</sup>  | 01/00-12/05  | Case-control study              | Mort. rate cases=60%<br>Mort. rate controls=28%<br>OR=6.2; 95%CI(1.7–22.1) | Spain    | 2 years           | 50 cases<br>50 controls   | age, sex, date of adm,<br>degree of air obstruction | no data   | Patients had COPD<br>the isolation sample was sputum |
| 3  | Micek 2015 <sup>280</sup>    | no data      | Multicentre retrospective study | Mort. rate cases=44.7%<br>Mort. rate controls=31.7%                        | World*   | hospitaliz        | 226 cases<br>514 controls | pneumonia   | median (IQR)<br>cases=27(14-56.3)<br>controls=25(13-46) | *USA, Europe (4 countries)                           |

|   |                                |             |                                 |   |                    |                            |  |           |   |  |
|---|--------------------------------|-------------|---------------------------------|---|--------------------|----------------------------|--|-----------|---|--|
|   |                                |             |                                 | HR=1.39; 95%CI(1.05-1.83)   |                    |                            |  |           |   |  |
| 4 | Pena 2013 <sup>281</sup>       | 01/06-12/11 | Retrospective study             | a) Mort. rate cases=15%<br>Mort. rate controls=29%<br>b) Mort. rate cases=50%<br>Mort. rate controls=55%        | Spain              | a) 7 days<br>b) hospitaliz | 60 cases<br>31 controls  | pneumonia | no data   |  |
| 5 | Tumbarello 2013 <sup>282</sup> | 01/08-12/10 | Retrospective study             | Mort. rate cases=59.5%<br>Mort. rate controls=35.2%<br>OR=2.69; 95%CI(1.14-6.43)                                | Italy              | in ICU                     | 42 cases<br>68 controls  | ICU       | no data   | patients were in ICU   |
| 6 | Yang 2009 <sup>283</sup>       | 10/02-04/06 | Prospective observational study | Mort. rate cases=35%<br>Mort. rate controls=29%   | San Francisco, USA | 28 days                    | 20 cases<br>55 controls  | VAP       | median (IQR)<br>cases=37(28.5-72)<br>controls=34(21-47) |  |
| 7 | Yayan 2015 <sup>284</sup>      | 01/04-08/14 | Retrospective study             | a) Mort. rate cases=28.6%<br>Mort. rate controls=23.8%<br>b) Mort. rate cases=7.4%<br>Mort. rate controls=18.5% | Germany            | hospitaliz                 | a) HAI<br>14 cases<br>63 controls<br>b) CAI<br>27 cases<br>64 controls | VAP       | no specific data  | data were extracted since presented from different prospective |

Table 62 and Table 63 present the results of studies that include patients with different sites of infection. Almost all the articles specify the number of cases for the different infection sites but do not report different mortalities based on the infection site. When it was possible the results are presented differentiating the mortality for each site of infection.

Table 62: Short extraction table of original articles on mortality of MDRPA infected patients vs non infected patients for different infection sites

| Nr | Author                            | Study Period | Study type                 | Outcome   | Location | Period of outcome          | Population              | Matching criteria               | LOS (days)        | Notes                |
|----|-----------------------------------|--------------|----------------------------|---|----------|----------------------------|-------------------------|---------------------------------|-------------------|----------------------|
| 1  | Aloush 2016 <sup>285</sup>        | no data      | Matched cohort study       | Mort. rate cases=21%<br>Mort. rate controls=12%<br>OR=4.4 | Israel   | hospitaliz                 | 82 cases<br>82 controls | ward, LOS, calendar time        | matching criteria |                      |
| 2  | Paramythiotou 2004 <sup>286</sup> | 01/99-12/00  | Matched case-control study | a) Mort. rate cases=44%<br>Mort. rate controls=47%        | Greece   | a) in ICU<br>b) hospitaliz | 34 cases<br>34 controls | severity of illness, LOS in ICU | in ICU<br>mean±SD | patients were in ICU |

|  |  |  |  |  |  |  |  |  |                                      |  |
|--|--|--|--|--|--|--|--|--|--------------------------------------|--|
|  |  |  |  | b) Mort. rate cases=47%<br>Mort. rate controls=50% |  |  |  |  | cases=11.1±18.6<br>controls=5.8±10.4 |  |
|--|--|--|--|--|--|--|--|--|--------------------------------------|--|

Table 63: Short extraction table of original articles on mortality of MDRPA infected patients vs MDSPA infected patients for different infection sites

| Nr | Author                        | Study Period | Study type                 | Outcome   | Location    | Period of outcome | Population                 | Matching criteria    | LOS (days)   | Notes  |
|----|-------------------------------|--------------|----------------------------|---|-------------|-------------------|----------------------------|----------------------|--|--|
| 1  | Cao 2004 <sup>287</sup>       | 01/99-12/02  | Retrospective cohort study | Mort. rate cases=54.5%<br>Mort. rate controls=16.2%   | China       | hospitaliz        | 44 cases<br>68 controls    | none                 | in ICU<br>mean(SD)<br>cases=21(47.7)<br>11(16.2)                       |  |
| 2  | da Matos 2016 <sup>288</sup>  | 01/10-02/12  | Retrospective cohort study | Mort. rate cases=70%<br>Mort. rate controls=58.9%<br>OR=1.6333;<br>95%CI(0.5043–5.2901)<br>Adults:<br>cases=81.3%<br>controls=71.4%<br>paediatric:<br>cases=25.0%<br>controls=55.0% | Brazil      | hospitaliz        | 20 cases<br>34 controls    | ICU                  | no specific data   | adults, children and neonates patients in ICU  |
| 3  | Morales 2012 <sup>289</sup>   | 01/05-12/06  | Retrospective study        | Mort. rate cases=24.6%<br>Mort. rate controls=12.8%<br>OR=1.77; 95%CI(1.41-2.22)  | Spain       | hospitaliz        | 134 cases<br>149 controls  | none                 | mean(SD), median<br>cases=25.1(16.1), 20<br>controls=39.0(30.3),<br>30 |  |
| 4  | Nathwan i 2014 <sup>290</sup> | 01/00-02/13  | Review and meta-analysis   | Mort. rate cases=25-60%<br>Mort. rate controls=7-50%<br>RR=2.34, 95%CI(1.53 – 3.57)   | World       | hospitaliz        | 559 cases<br>7881 controls |                      |  |  |
| 5  | Ortega 2004 <sup>291</sup>    | 01/01-12/01  | Prospective study          | Mort. rate cases=22%<br>Mort. rate controls=23%   | Netherlands | in ICU            | 18 cases*<br>35 controls** | underlying condition | In ICU<br>median (range)<br>cases=18(0-40)<br>controls=10(0-44)        | all patients were critically ill<br>*resistant of at least 2 antibiotics<br>**susceptible or |

|   |                          |             |                                   |  |       |            |                           |      |   |  |
|---|--------------------------|-------------|-----------------------------------|--|-------|------------|---------------------------|------|---|--|
|   |                          |             |                                   |  |       |            |                           |      |   | resistant to only 1 antibiotic               |
| 6 | Peng 2014 <sup>292</sup> | 07/08-12/12 | Case-control study                | Mort. rate cases=26.1%<br>Mort. rate controls=12.5%  | China | hospitaliz | 188 cases<br>168 controls | none | median (range)<br>cases=35(5-697)<br>controls=24(1-262) | it was a surveillance study                  |
| 7 | Su 2016 <sup>293</sup>   | 01/03-06/15 | Retrospective double centre study | a) Mort. rate cases=36%<br>Mort. rate controls=31.0%<br>b) Mort. rate cases=47.6%<br>Mort. rate controls=37.9% | China | 30 days    | 25 cases<br>29 controls   | none | no specific data  | a) related mortality<br>b) overall mortality |

This literature research was specific in the searching strings and we did not detect many unspecific articles. The introduction of the term mortality excluded many ineligible studies. The vast majority of papers contained related information to mortality but very often they did not report a comparison group.

Many studies reported treatment options for the resistant infections, but since they used just cases infected with MRDPA and no control group, as defined by our eligibility criteria, these were excluded.

All studies were performed in healthcare settings, although some report cases of infection that originated in the community; only one study treated only patients with infection onset in the community.

The studies that included patients with MDRPA which were all also resistant to carbapenems were also not included in this review since the mortality reported in these cases is not only attributable to the multidrug resistance but also to the carbapenem resistance.

The only exception is the meta-analysis reported in Table 63 from Nathwani et al 2014<sup>290</sup> which included patients resistant to carbapenems.

## 14. Penicillin resistant *Streptococcus pneumoniae*

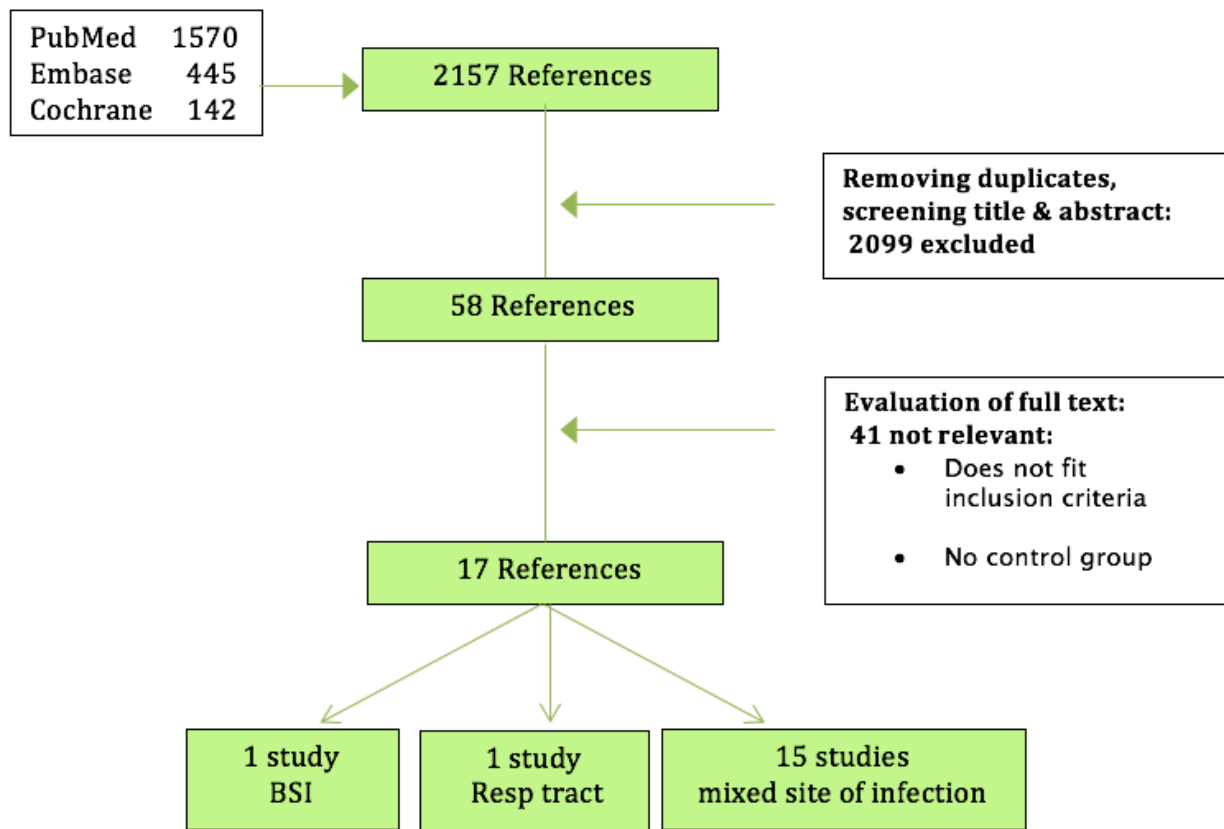
To research the attributable case fatality and the attributable LOS to penicillin resistant *Streptococcus pneumoniae* (PRSP) we searched the following databases: PubMed, EMBASE and Cochrane Database of Systematic Reviews. We performed an advanced search on Pubmed using MeSH term “*Streptococcus pneumoniae*” and all fields “penicillin resistant”. Embase was searched for “penicillin resistant” AND *streptococcus pneumoniae*. An advanced search on the Cochrane Library was performed using terms “*streptococcus pneumoniae*” and “penicillin”. No language restrictions were made, and filter for research in humans was applied.

Relevant data were extracted and retrospective extraction tables are shown in the results section.

The flow diagram shown in Figure 14 describes the steps in the literature review of penicillin resistant *Streptococcus pneumoniae*.

Once identified, the studies reporting relevant data were grouped based on the site of infection. All studies compared penicillin-resistant *Streptococcus pneumoniae* (PRSP) with penicillin-susceptible *Streptococcus pneumoniae* (PSSP). No studies were found with non-infected patients as comparator.

Figure 14: Search for studies on Penicillin resistant *Streptococcus pneumoniae*. Inclusion and exclusion diagram.



One systematic review and meta-analysis was found<sup>294</sup>.

The following tables include studies reporting results for BSI, respiratory tract and mixed site of infection, based on the comparison group they used. All information is reported as was presented in the original papers.

Table 64. Short extraction table of original articles on meningitis mortality of PRSP infected patients vs PSSP patients.

| Nr | Author                 | Study Period | Study type                                      | Outcome  | Location | Period of outcome           | Population               | Matching criteria | LOS (days) |
|----|------------------------|--------------|---|--|----------|-----------------------------|--------------------------|-------------------|------------|
| 1  | Yu 2003 <sup>295</sup> | 12/98-01/01  | Prospective, international, observational study | Mort. rate case=23.7%<br>Mort. rate controls=15.1% | Global   | >14 days after onset of BSI | 76 cases<br>598 controls | N/A               | N/A        |

Table 65. Short extraction table of original articles on BSI mortality of PRSP infected patients vs PSSP patients.

| Nr | Author                       | Study Period | Study type                      | Outcome   | Location | Period of outcome               | Population              | Matching criteria | LOS (days) | Notes   |
|----|------------------------------|--------------|---------------------------------|---|----------|---------------------------------|-------------------------|-------------------|------------|---|
| 1  | Watanabe 2000 <sup>296</sup> | 12/92-05/97  | Retrospective comparative study | a)Mort. rate case=0%<br>Mort. rate controls=8%<br>b) Mort. rate case=12.5%<br>Mort. rate controls=20% | Japan    | 7 days after start of treatment | 24 cases<br>25 controls | N/A               | N/A        | a) infection related mortality<br>b) mortality due to complications |

Table 66. Short extraction table of original articles on pneumonia mortality of PRSP infected patients vs PSSP patients.

| Nr | Author                               | Study Period | Study type                 | Outcome   | Location            | Period of outcome   | Population                       | Matching criteria | LOS (days)  | Cost (US dollars)                    |
|----|--------------------------------------|--------------|----------------------------|---|---------------------|---|----------------------------------|-------------------|---|--------------------------------------|
| 1  | Gouveia 2011 <sup>297</sup>          | 1996 - 2006  | Observational study        | Mortality:<br>adjusted hazard ratio*:<br>1.62 (1.08-2.43)   | Salvador, Brazil    | hospitaliz  | 93 cases<br>548 Total population | N/A               | N/A   |                                      |
| 2  | Reechaipichitkul 2006 <sup>298</sup> | 01/95-12/04  | Cross-sectional study      | a)Mort. rate case=9.1%<br>Mort. rate controls=11.9%<br>b)Mort. rate case=9.1%<br>Mort. rate controls=9.5% | Khon Kaen, Thailand | Hospitalization<br>a) all-cause mortality<br>b) pneumonia related mortality | 22 cases<br>42 controls          | N/A               | Mean(SD)<br>R: 12 (9)<br>S: 15.5 (17.7)<br>p=0.43 |                                      |
| 3  | Sun 2006 <sup>299</sup>              | 1999 – 2003  | Retrospective cohort study | Mort. rate case=9%<br>Mort. rate controls=14%   | Connecticut, USA    | Hospitalization   | 44 cases<br>168 controls         | N/A               | N/A   | Median<br>R: \$10,809 (6,118-22,209) |



|    |                                |             |                                  |   |                  |   |  |  |   |   |
|----|--------------------------------|-------------|----------------------------------|---|------------------|---|--|--|---|---|
|    |                                |             |                                  |   |                  |   | (cases are non-susceptible)                |  |   | S: (\$8,503) (5,452-15,862)                     |
| 4  | Song 2004 <sup>300</sup>       | 01/00-06/01 | Retrospective study              | Mort. rate case=16%<br>Mort. rate controls=12.4%<br>OR=1.3; 95%CI(0.5-3.4)                                  | Asia             | 30 days after diagnosis   | 69 cases<br>105 controls                   | N/A  | N/A                                       | N/A   |
| 5  | Einarsson 1998 <sup>301</sup>  | 1988 – 1994 | Retrospective case-control study | Mort. rate case=11%<br>Mort. rate controls=5.5%   | Iceland          | not defined but most probably mortality in hospital                         | 36 cases<br>36 controls                    | Age, gender, hospitalised at the same time | Mean Case: 26.8<br>Control 11.5 (p=0.001) | Average pharmacy costs \$736 vs. \$213 (p<0.01) |
| 6  | Sangthawan 2003 <sup>302</sup> | 1998-2001   | Prospective study                | Mort. rate case=36.8%<br>Mort. rate controls=18.5%  | Thailand         | not defined but most probably mortality in hospital                         | 19 cases<br>27 controls                    | N/A  | N/A                                       | N/A   |
| 7  | Falco 2004 <sup>303</sup>      | 1997-2001   | Retrospective and prospective    | a)Mort. rate case=26.7%<br>Mort. rate controls=12.7%<br>b)Mort. rate case=13.3%<br>Mort. rate controls=9.9% | Barcelona, Spain | Hospitalization<br>a) all-cause mortality<br>b) pneumonia related mortality | 15 cases<br>181 controls                   | N/A  | N/A                                       | N/A   |
| 8  | Pallares 1995 <sup>304</sup>   | 1984 – 1993 | Prospective study                | Mort. rate case=27.6%<br>Mort. rate controls=21.8%<br>aOR=1.0; 95%CI(0.5-1.9)                               | Barcelona, Spain | Within one month of discharge   | 47 cases<br>440 controls                   | N/A  | N/A                                       | N/A   |
| 9  | Ewig 1999 <sup>305</sup>       | 1996 – 1998 | Prospective study                | Mort. rate case=18%<br>Mort. rate controls=5.8%   | Barcelona, Spain | Hospitalization   | 33 cases<br>52 controls                    | N/A  | N/A                                       |   |
| 10 | Aspa 2014 <sup>306</sup>       | 01/99-04/00 | Prospective multi-centre study   | Mort. rate case=18.3%<br>Mort. rate controls=12.2%  | Spain            | 30 days   | 64 cases<br>409 controls                   | N/A  | No data                                   | N/A   |
| 11 | Feikin 2000 <sup>307</sup>     | 1995 – 1997 | Population-based                 | a) OR= 1.3; 95%CI(0.5-3.7)  | USA              | 30 days<br>a) resistant   | a) 37 cases<br>b) 20 cases<br>383 controls | N/A  | No data                                   | N/A   |

|    |                              |             |                          |  |                  |   |   |     |         |     |
|----|------------------------------|-------------|--------------------------|--|------------------|---|---|-----|---------|-----|
|    |                              |             | surveillance study       | b) OR=2.3 ; 95%CI(0.7-7.4)   |                  | b) highly resistant, MIC>4  |   |     |         |     |
| 12 | Tleyjeh 2006 <sup>294</sup>  | Up to 01/05 | Review and meta-analyses | a) Mort. rate non susceptible=19.4%<br>Mort. rate controls=15.7%<br>b)OR non-susceptible=1.3; 95%CI(1.08–1.59)<br>OR intermediate=1.34; 95% CI(1.13–1.60)<br>OR resistant=1.29; 95% CI(1.01–1.66)<br>c) aRR non susceptible=1.29; 95%CI(1.04–1.59) | World            | different based on the included studies<br>a) pooled mortality rate<br>b) all-cause mortality<br>c) combined adjusted (6 studies) | 10 studies (some included also non susceptible) | N/A | No data | N/A |
| 13 | Yigla 1995 <sup>308</sup>    | 11/89-04/90 | Prospective study        | Mort. rate case=43%<br>Mort. rate controls=33%   | Israel           | Hospitalization   | 7 cases<br>15 controls                          | N/A | No data | N/A |
| 14 | Pallares 2002 <sup>309</sup> | 01/94-10/00 | Prospective study        | Mort. rate case=43%<br>Mort. rate controls=20.3%   | Barcelona, Spain | 30 days   | 77 cases<br>300 controls                        | N/A | No data | N/A |
| 15 | Jehl 2002 <sup>310</sup>     | 09/98-04/00 | Prospective survey       | a)Mort. rate case=8.3%<br>Mort. rate controls=3.5%<br>b)Mort. rate case=4.2%<br>Mort. rate controls=10.4%<br>c)Mort. rate case=12.5%<br>Mort. rate controls=13.9%  | France           | a) 3 days<br>b) 30 days<br>c) total   | 49 cases<br>246 controls                        | N/A | No data | N/A |

\*After adjusting for age group, PR pneumococcal meningitis cases had higher case fatality than cases caused by penicillin-susceptible organisms

There was a limited number of case-control studies reporting outcomes of interest. Many studies reviewed penicillin non-susceptible *Streptococcus pneumoniae* (including intermediately resistant and resistant) rather than solely penicillin-resistant *Streptococcus pneumoniae*. The majority of infections in the non-susceptible group fall into the intermediate categories. Most evidence indicates that standard treatment with a beta-lactam antimicrobial is effective against pneumococcal pneumonia caused by strains with penicillin MIC <2, thus including these studies may skew the results and they were excluded.

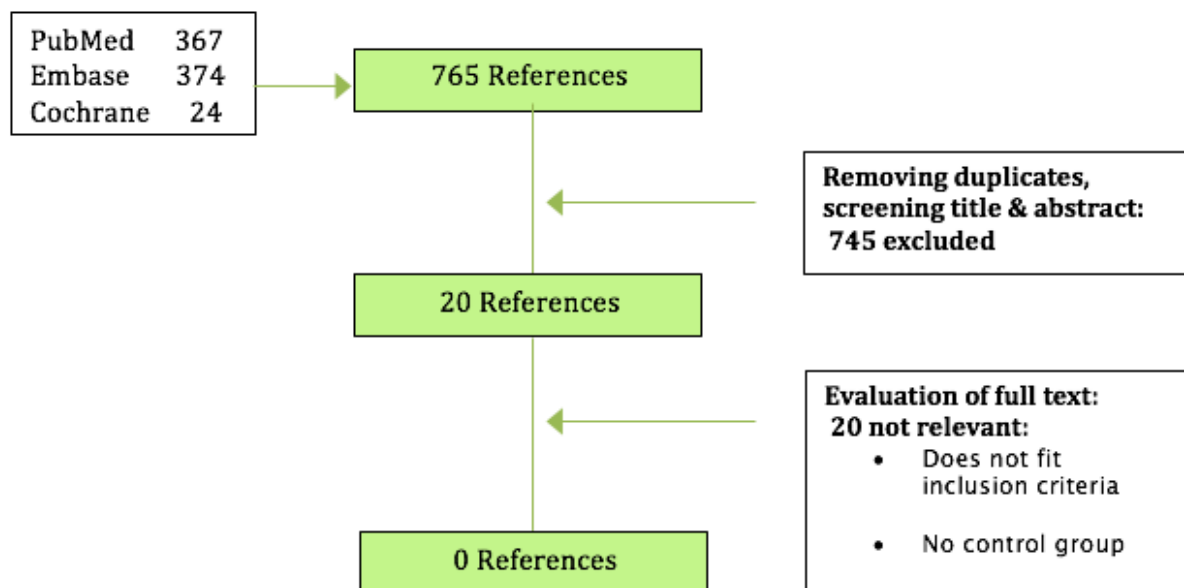
In January 2008 the Clinical and Laboratory Standards Institute revised the penicillin susceptibility breakpoints for non-meningeal pneumococcal infections from <0.06 micrograms/ml to <2 micrograms/ml<sup>311</sup>. Most studies found, however, predate this change but were not excluded and may represent a limitation when applied to incidence data from EARS-Net.

## **15. Penicillin and macrolide resistant *Streptococcus pneumoniae***

To research the attributable case fatality and the attributable LOS to penicillin and macrolide resistant *Streptococcus pneumoniae* (PMRSP) the following databases were searched: PubMed, EMBASE and Cochrane Database of Systematic Reviews. We performed an advanced search on Pubmed using MeSH term “*Streptococcus pneumoniae*” and all fields “penicillin and macrolide resistant”. Embase was searched for “penicillin and macrolide resistant” AND *streptococcus pneumoniae*. An advanced search on the Cochrane Library was performed using terms “*streptococcus pneumoniae*” and “penicillin and macrolide”. No language restrictions were made and filter for research in humans was applied.

The following flow diagram in Figure 15 describes the steps in the literature review of penicillin resistant *Streptococcus pneumoniae*.

Figure 15: Search for studies on Penicillin- and macrolide-resistant *Streptococcus pneumoniae*. Inclusion and exclusion diagram.



Unfortunately, no studies were found which focused solely on penicillin and macrolide resistant *Streptococcus pneumoniae*. Studies were available for penicillin resistant *streptococcus pneumoniae* and macrolide resistant *streptococcus pneumoniae* individually.

## 16. Vancomycin resistant *Enterococcus faecalis* and *faecium*

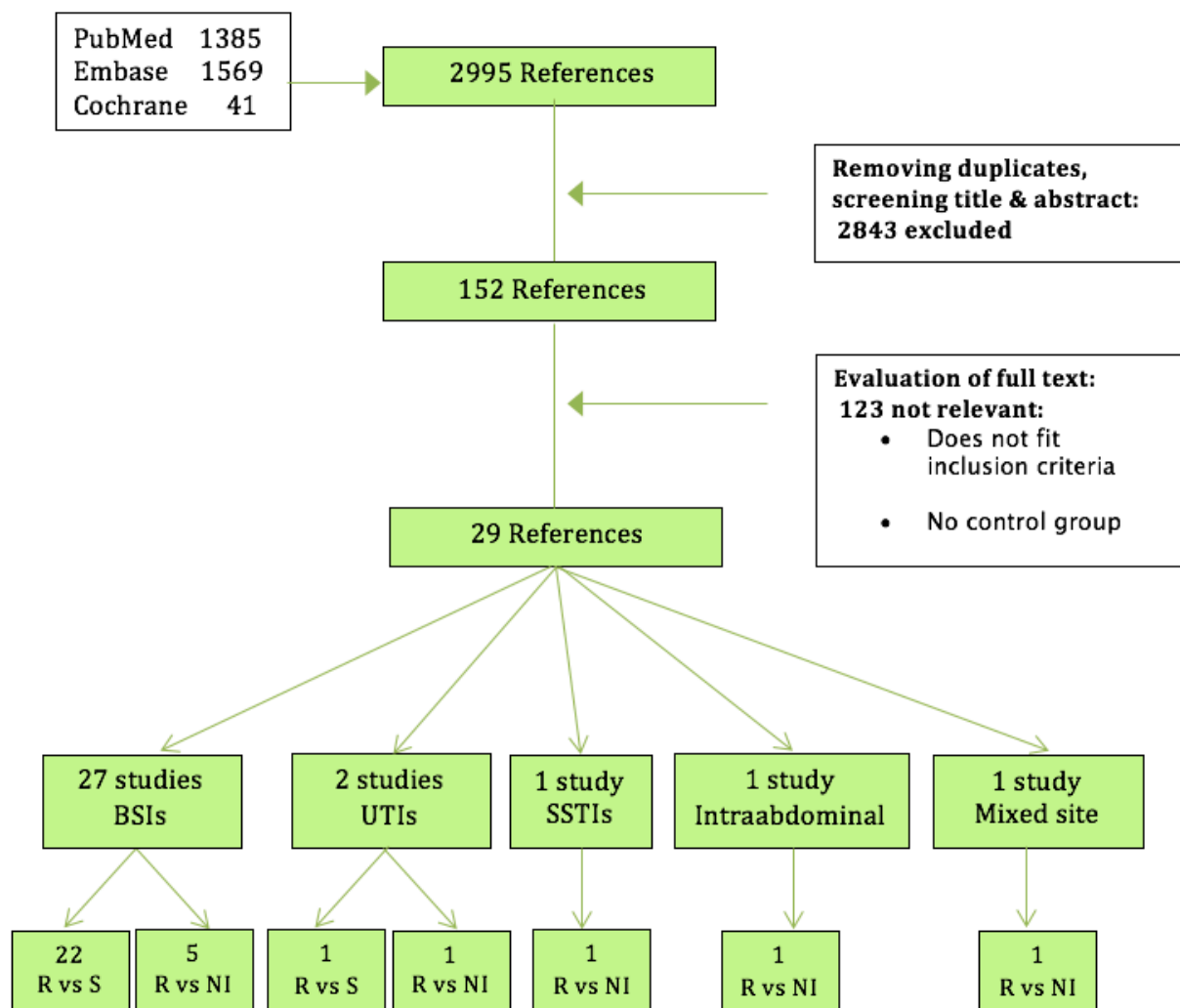
To research the attributable case fatality and the attributable LOS to vancomycin resistant *Enterococcus faecalis* and *faecium* (VRE), we searched the following databases: PubMed, EMBASE and Cochrane Database of Systematic Reviews. We performed an advanced search on Pubmed using MeSH term “Enterococcus faec\*” and all fields “vancomycin-resistant”. Embase was searched for “vancomycin resistant” AND “enterococcus faec\*”. An advanced search on the Cochrane Library was performed using terms “enterococcus faec\*” and “vancomycin”. No language restrictions were made, and filter for research in humans was applied.

Relevant data were extracted from relevant studies identified during the literature search using a standardised data extraction form.

The following flow diagram describes the steps in the literature review of vancomycin-resistant *Enterococcus*.

Once identified the studies reporting relevant data were grouped based on the site of infection. All eligible studies reported a VRE infected group and a control group. The latter could represent NI or S infections.

Figure 16: Search for studies on Vancomycin resistant *Enterococcus faecalis* or *faecium*. Inclusion and exclusion diagram.



The sum of the studies categorised for infection site is higher than the total of 29 eligible studies because one study, Carmeli et al. 2002<sup>312</sup>, reported specific data for different infection sites, therefore was categorised three times.

In addition, two meta-analyses reviewing bacteraemia were found and the references included in the systematic reviews were hand-searched for further primary studies missed in the literature search<sup>313,314</sup>.

The following tables include studies reporting results for BSIs, UTIs, SSTIs and other infections from VRE, based on the comparison group they used. All information is reported as was presented in the original papers. All the included studies reported at least one health or economic outcome of interest.

Table 67. Short extraction table of original articles on BSI mortality of VRE infected patients vs. VSE patients.

| Nr | Author                       | Study Period | Study type                         | Outcome   | Location        | Period of outcome  | Population                | Matching criteria   | LOS (days)   | Cost per admission |
|----|------------------------------|--------------|------------------------------------|---|-----------------|--|---------------------------|---|--|--------------------|
| 1  | Da Silva 2014 <sup>315</sup> | 1998 - 2008  | Retrospective cohort study         | OR 2.73; 95% CI: 1.09-7.78  | Brazil          | In-hospital  | 30 cases<br>284 controls  | same unit and time interval                                       | N/A  | N/A                |
| 2  | Yoo 2005 <sup>316</sup>      | 2000 – 2001  | Retrospective cohort study         | Mort. rate cases=78.9%<br>Mort. rate controls=62.5%   | Seoul           | Post-discharge   | 19 cases<br>8 controls    | same time period  | Mean Case 56.2 (28.2)<br>Control 22.9 (13.3)                     | N/A                |
| 3  | Lodise 2002 <sup>317</sup>   | 1996 – 2000  | Retrospective matched case-control | a)Mort. rate cases=52.8%<br>Mort. rate controls=26.4%<br>aOR=4.0; 95%CI(1.2–13.3)<br>a)Mort. rate cases=37.7%<br>Mort. rate controls=20.8%<br>aOR=5.2; 95%CI(1.4-2.0) | Michigan, USA   | 7 days<br>a) all-cause mortality<br>b) infection related mortality | 53 cases<br>53 controls   | age, APACHE score at onset, admitting service, LOS prior to onset | Mean Case 22.7 (1.88)<br>Control 15.9 (1.7)<br>(after diagnosis) | N/A                |
| 4  | Peset 2000 <sup>318</sup>    | 1994 – 1996  | Prospective case-control           | Mort. rate cases=23.5%<br>Mort. rate controls=12.4%<br>OR=2.7; 95%CI(0.47–7.89)   | Valencia, Spain | In-hospital  | 17 cases<br>169 controls  | Controls selected consecutively                                   | Mean Case: 74.75 (46.27)<br>Control 47.26 (37.59)                | N/A                |
| 5  | Garbutt 2000 <sup>319</sup>  | 1995 – 1997  | Retrospective cohort               | a)Mort. rate cases=48%<br>Mort. rate controls=30%<br>OR=1.74; 95%CI(0.50–6.12)<br>b)Mort. rate cases=43%<br>Mort. rate controls=36%<br>OR=1.28; 95%CI(0.47–3.51)      | Missouri, USA   | In-hospital  | 46 cases<br>23 controls   |   | Mean Case: 39.7<br>Control: 20.9                                 | N/A                |
| 6  | Bhavnani 2000 <sup>320</sup> | 1995 – 1997  | Multicentre, case-control          | a)Mort. rate cases=52%<br>Mort. rate controls=27%<br>aOR=3.34; 95%CI(1.61-6.91)<br>b)Mort. rate cases=32%   | USA             | Within 30-days of BSI  | 150 cases<br>150 controls | Time of occurrence and  | N/A  | N/A                |

|    |                             |             |                                       |  |                 |   |                           |   |   |   |
|----|-----------------------------|-------------|---------------------------------------|--|-----------------|---|---------------------------|---|---|---|
|    |                             |             |                                       | Mort. rate controls=17%  |                 |   |                           | enterococcal species                              |   |   |
| 7  | Lucas 1998 <sup>321</sup>   | 1991 – 1996 | Case-control                          | Mort. rate cases=45%<br>Mort. rate controls=27%<br>aOR=2.07; 95%CI(0.96-4.42)  | Baltimore, USA  | In-hospital   | 93 cases<br>101 controls  | Timing  | Mean<br>Case: 49.1<br>(48.3)<br>Control: 38.6<br>(31.2) | N/A   |
| 8  | Stosor 1998 <sup>322</sup>  | 1992 – 1995 | Retrospective comparison              | a) Mort. rate cases=76%<br>Mort. rate controls=41%<br>b)Mort. rate cases=38%<br>Mort. rate controls=9%<br>c)Mort. rate cases=24%<br>Mort. rate controls=19%<br>d)Mort. rate cases=14%<br>Mort. rate controls=13% | Chicago, USA    | In-hospital<br>a) overall mortality<br>b) infection directly related mortality<br>c) infection indirectly related mortality<br>d) unrelated mortality | 21 cases<br>32 controls   |   | Mean<br>Case: 34.8<br>(23.3)<br>Control 16.7<br>(16.1)  | Case<br>\$83,897<br>Control<br>\$56,707<br>Excess cost:<br>\$27,190 |
| 9  | Linden 1996 <sup>323</sup>  | 1991 – 1994 | Retrospective cohort                  | a)Mort. rate cases=57%<br>Mort. rate controls=35%<br>aRR=3.47(1.47-8.19)<br>b)Mort. rate cases=46%<br>Mort. rate controls=25%  | Pittsburgh, USA | In-hospital a) all-cause mortality<br>b) infection related mortality  | 54 cases<br>48 controls   | Liver transplant patients with VREF or VSEF       | Median: Case<br>46<br>Control 19<br>After diagnosis     | N/A   |
| 10 | Krcmery 2001 <sup>324</sup> |             | Retrospective review                  | Mort. rate cases=22%<br>Mort. rate controls=41.3%  | Slovak Republic |   | 9 cases<br>92 controls    |   | N/A   | N/A   |
| 11 | Vergis, 2000 <sup>325</sup> | 1995-1997   | Prospective multicentre observational | Mort. rate cases=33%<br>Mort. rate controls=11%<br>aOR=2.1(1.14-3.88)  | USA             | 14 days from 1st positive BC  | 147 cases<br>251 controls |   | N/A   | N/A   |
| 12 | Shay 1995 <sup>326</sup>    | 1991 – 1993 | Retrospective case- control           | Mort. rate cases=33%<br>Mort. rate controls=6.5%<br>aOR=3.3(0.7-15)  | NY, USA         |   | 46 cases<br>46 controls   | Randomly selected control pts during study period | N/A   | N/A   |
| 13 | Wells 1995 <sup>327</sup>   | 1994        | Retrospective case-control            | Mort. rate cases=17%<br>Mort. rate controls=27%  | USA             | In-hospital   | 6 cases<br>37 controls    | Same time period                                  | N/A   | N/A   |
| 14 | Cheah 2013 <sup>328</sup>   | 2002 – 2010 | Retrospective matched cohort          | Mort. rate cases=36%<br>Mort. rate controls=26%<br>aOR=1.21; 95%CI(0.52-2.79)  | Australia       | In-hospital   | 116 cases<br>116 controls | Date and unit of admission                        | Median excess<br>4.89 (0.56 – 11.52)                    | Excess cost:<br>Australia<br>n \$<br>28,872                         |

|    |                                     |             |                          |   |                |  |   |                           |  |     |
|----|-------------------------------------|-------------|--------------------------|---|----------------|--|---|---------------------------|--|-----|
| 15 | DiazGranados 2005 <sup>329</sup>    | 1994 – 2001 | Retrospective cohort     | Mort. rate cases=63.6%<br>Mort. rate controls=41%<br>aHR=4.97; 95%CI(1.21-20.44)  | Atlanta, USA   | 60 days from BSI   | 22 cases<br>61 controls                               | Patients with neutropenia | Median Case: 42 (24-75)<br>Control 31 (2-72)   | N/A |
| 16 | Peel 2012 <sup>330</sup>            | 2000-2009   | Case-case-control        | Mort. rate resistant=37.5%<br>Mort. rate sensitive=23.8%<br>Mort. rate NI=2.5%  | Australia      |  | 80 resistant<br>80 sensitive<br>80 NI                 | Time                      | N/A  | N/A |
| 17 | Mainous 1997 <sup>331</sup>         | 1992 – 1994 | Retrospective cohort     | Mort. rate cases=40%<br>Mort. rate controls=39%   | Baltimore, USA | In-hospital  | 10 cases<br>31 controls                               | Stay in SICU              | mean (SD)<br>cases=28 (18)<br>controls=12 (10) | N/A |
| 18 | Salgado 2003 <sup>314</sup>         | 01/86-04/02 | Review and Meta-analyses | a)Mort. rate cases=41.5(0-66.7)%<br>Mort. rate controls=47.8(17-100)%<br>b)Mort. rate cases=45.2%<br>Mort. rate controls=19.0%<br>RR=2.38; 95%CI(2.13-2.66)<br>c)Mort. rate cases=48.9%<br>Mort. rate controls=19%<br>RR=2.57; 95%CI(2.27-2.91)<br>d)Mort. rate cases=28.7%<br>Mort. rate controls=10.9%<br>RR=2.62; 95%CI(1.84-3.73)<br>e)Mort. rate cases=39.1%<br>Mort. rate controls=21.8%<br>RR=1.79; 95%CI(1.28-1-5)<br>f) Attributable mortality =17-46% | World          | a)crude mortality rates of pooled cases (14 studies) and controls (26 studies)<br>b) pooled cases and controls from 13 studies<br>c) pooled cases and controls from 9 studies with higher sample size<br>d) pooled cases and controls from 5 studies with infection related mortality<br>e) studies of point d) excluded one that was producing heterogeneity<br>f) range of values from 4 studies which matched for severity of illness | 856 cases<br>1180 controls                            |                           | Excess of total stay of VRE vs VSE=10-46 days  | N/A |
| 19 | DiazGranados 2005(b) <sup>313</sup> | Up to 03/03 | Review and Meta-analyses | OR=2.52; 95%CI(1.9–3.4)   | World          | N/A  | 683 cases<br>891 controls (pooled cases and controls) | Severity of illness       | N/A  | N/A |



|    |                                |             |                            |   |     |  |                           |      |  |     |
|----|--------------------------------|-------------|----------------------------|---|-----|--|---------------------------|------|--|-----|
|    |                                |             |                            |   |     |  | from 9 studies)           |      |  |     |
| 20 | CDC 1993 <sup>332</sup>        | 01/89-03/93 | Surveillance study         | Mort. rate cases=36.6%<br>Mort. rate controls=16.4% | USA | not specified, but most probably mortality in hospital | 71 cases<br>1810 controls |      | N/A  | N/A |
| 21 | Lautenbach 1999 <sup>333</sup> | 01/93-12/95 | Historical cohort study    | Mort. rate cases=45.8%<br>Mort. rate controls=33.5% | USA | not specified, but most probably mortality in hospital | 72 cases<br>188 controls  | Unit | median (range)<br>cases= 23<br>(19.18-27.82)<br>controls= 12<br>(9.0-15.0) | N/A |
| 22 | Stroud 1996 <sup>334</sup>     | 01/89-06/93 | Retrospective cohort study | Mort. rate cases=69%<br>Mort. rate controls=76%     | USA | not specified, but most probably mortality in hospital | 26 cases<br>119 controls  |      | overall cases+controls<br>mean(range)=8<br>1(9-583)<br>median=60           | N/A |

Table 68. Short extraction table of original articles on BSI mortality of VRE infected patients versus NI

| Nr | Author                      | Study Period | Study type                            | Outcome   | Location       | Period of outcome | Population                | Matching criteria | LOS (days)   | Cost per admission       |
|----|-----------------------------|--------------|---------------------------------------|---|----------------|-------------------|---------------------------|-------------------|--|--------------------------|
| 1  | Song 2003 <sup>335</sup>    | 1993 - 2000  | Population-based matched cohort study | Mort. rate cases=50.3%<br>Mort. rate controls=27.7%<br>aOR=3.04; 95%CI(1.66-5.53) | Baltimore, USA | In-hospital       | 159 cases<br>159 controls | *                 | Median<br>Case 53<br>Control 28                        | Excess cost<br>\$81,208  |
| 2  | Carmeli 2002 <sup>312</sup> | 1993 - 1997  | Matched cohort study                  | RR= 12.3<br>Attributable mortality=25%  | USA            | In-hospital       | 233 cases<br>647 controls | **                | Multiplicative effect: 2.06<br>Attributable days<br>15 | Attributable<br>\$13,537 |

|   |                            |             |                                    |   |               |             |   |                       |  |  |
|---|----------------------------|-------------|------------------------------------|---|---------------|-------------|---|-----------------------|--|--|
| 3 | Edmond 1996 <sup>336</sup> | 1993 – 1995 | Matched retrospective cohort study | Mort. rate cases=67%<br>Mort. rate controls=30%<br>OR=2.3; 95%CI(1.2-4.1)       | USA           | In-hospital | 27 cases<br>27 controls                   | ***                   | N/A  | N/A  |
| 4 | Edmond 1995 <sup>337</sup> | 1993        | Pairwise matched case-control      | Mort. rate cases=73%<br>Mort. rate controls=30%                                 | USA           | In-hospital | 11 cases<br>22 controls                   | ****                  | Mean Case: 74.75±<br>46.27<br>Control: 47.26±<br>37.59                           | N/A  |
| 5 | Butler 2010 <sup>338</sup> | 2002-2003   | Retrospective cohort               | Mort. rate resistant= 32%<br>Mort. rate sensitive=17%<br>Mort. rate controls=4% | Missouri, USA | In-hospital | 94 resistant<br>182 sensitive<br>20150 NI | Non-surgical patients | Attributable LOS<br>VRE: 2.2 (1.7-2.7)<br>Attributable LOS<br>VSE: 1.1 (0.9-1.4) | Attributable costs<br>VRE: \$4,036<br>(3,170-5,140)<br>VSE: \$2,023<br>(1,588-2,575) |

\*matched based on age, year of admission, exposure time, same principle diagnosis at admission, same primary procedure, same APR-DRGs, subgroup of matched case-patients and control patients who had the same APR-DRG complexity level.

\*\* hospital ward, calendar date (within 7 days), duration of hospital stay at time of matching, up to three controls for each case.

\*\*\*control hospitalised during same period and at least as long as case patient; matched for underlying disease, matched for age within 10 years, matched for gender, matched for surgical procedure.

\*\*\*\*hospitalised on oncology unit during study period. Underlying haematological disorder, hospitalised for at least as long as matched case patient had been up until 1<sup>st</sup> BC yielded VREF.

Five studies reported mortality for patients with VRE BSI compared with no infection. Two of these studies undertook a multivariate analysis adjusting for severity of illness.

One study was found for UTI mortality for patients with VRE versus VSE. This study only reported mortality and no other outcome of interest.

Table 69: Short extraction table of original articles on UTI mortality of VRE infected patients versus VSE patients.

| Author                    | Study Period | Study type               | Outcome  | Location      | Period of outcome | Population               | Matching criteria | LOS (days)   |
|---------------------------|--------------|--------------------------|--|---------------|-------------------|--------------------------|-------------------|--|
| Khair 2013 <sup>339</sup> | 2011         | Prospective cohort study | Mort. rate cases=14%<br>Mort. rate controls=7% | Missouri, USA | In-hospital       | 74 cases<br>180 controls | N/A               | after bacteremia<br>mean (range)<br>cases= 6.8(0.1-150.8)<br>controls= 5(0.2-78.2) |

One study was found for reporting mortality, LOS and cost for patients with VRE UTIs, SSTIs and VRE intraabdominal infection versus non-infected patients (NI).

Table 70. Short extraction table of original articles on UTI mortality of VRE infected patients versus NI patients.

| Author                      | Study Period | Study type           | Outcome*                            | Location | Period of outcome | Population                | Matching criteria | LOS (days)**                     | Cost per admission    |
|-----------------------------|--------------|----------------------|-------------------------------------|----------|-------------------|---------------------------|-------------------|----------------------------------|-----------------------|
| Carmeli 2002 <sup>312</sup> | 1993 – 1997  | Matched cohort study | RR: 4.28<br>Attributable to VRE: 9% | USA      | In-hospital       | 233 cases<br>647 controls | ***               | ME:1.75<br>Attributable 5.4 days | Attributable: \$6,665 |

\*Adjusted mortality reported as RR and attributable percentage

\*\*Study reported LOS as ME (multiplicative effect) and attributable days

\*\*\*hospital ward, calendar date (within 7 days), duration of hospital stay at time of matching, up to three controls for each case.

Table 71. Short extraction table of original articles on SST mortality of VRE infected patients versus NI patients.

| Author                      | Study Period | Study type           | Outcome*                            | Location | Period of outcome | Population                | Matchin g criteria | LOS (days)**                      | Cost per admission     |
|-----------------------------|--------------|----------------------|-------------------------------------|----------|-------------------|---------------------------|--------------------|-----------------------------------|------------------------|
| Carmeli 2002 <sup>312</sup> | 1993 – 1997  | Matched cohort study | RR: 2.00<br>Attributable to VRE: 6% | USA      | In-hospital       | 233 cases<br>647 controls | ***                | ME: 1.78 Attributable<br>6.2 days | Attributable: \$13,884 |

\*Adjusted mortality reported as RR and attributable percentage

\*\*Study reported LOS as ME (multiplicative effect) and attributable days

\*\*\* hospital ward, calendar date (within 7 days), duration of hospital stay at time of matching, up to three controls for each case.

Table 72. Short extraction table of original articles on intraabdominal infection of VRE infected patients versus NI patients.

\*Adjusted mortality reported as RR and attributable percentage

| Author                      | Study Period | Study type           | Outcome*                            | Location | Period of outcome | Population                | Matching criteria | LOS (days)**                      | Cost per admission     |
|-----------------------------|--------------|----------------------|-------------------------------------|----------|-------------------|---------------------------|-------------------|-----------------------------------|------------------------|
| Carmeli 2002 <sup>312</sup> | 1993 – 1997  | Matched cohort study | RR: 3.75<br>Attributable to VRE: 3% | USA      | In-hospital       | 233 cases<br>647 controls |                   | ME: 1.42 Attributable<br>2.6 days | Attributable: \$22,896 |

\*\*\*Study reported LOS as ME (multiplicative effect) and attributable days

Table 73. Short extraction table of original articles of VRE infected patients versus NI patients for mixed site of infection

| Author                           | Study Period | Study type         | Outcome  | Location | Period of outcome   | Population              | Matching criteria                             | LOS (days)  | Cost per admission |
|----------------------------------|--------------|--------------------|--|----------|---|-------------------------|---|---|--------------------|
| Tornieporth, 1996 <sup>340</sup> | 1990-1992    | Case control study | a)Mort. rate cases=37%<br>Mort. rate controls=19%<br>b)Mort. rate cases=58%<br>Mort. rate controls=43% | NY, USA  | In-hospital<br>a) overall mortality<br>b) ICU admitted patients mortality | 24 cases<br>23 controls | VSEF isolates within 1 month of VREF isolates | mean (range)<br>cases=64.5 (2-290)<br>controls=40.8 (2-248)<br>median<br>cases= 48<br>controls=26 | N/A                |

The most recent published eligible study found was in 2014 with studies found dating back to 1995. A limited number of studies focused solely on *Enterococcus faecium* and *faecalis* but rather more generally on enterococcal species. These two species do however constitute the majority of VRE infections.

## Conclusions

The literature reviews conducted to determine the attributable case fatality and the attributable length of stay due to the selected resistant bacterial infections have detected 281 original articles eligible for the purposes of the project. These peer reviewed publications vary based, amongst other, for the underlying study design, type of patients, time of outcome, control for adjusting and confounding variables, unit or set of study.

As described in the objectives of our literature review, for each pathogen/resistance combination we categorized the detected studies based on the site of infection and on the control group they used to compare the cases with the resistant infection.

We noticed a wide difference between the studies identified in our search. Many are limited to specific healthcare services (e.g. ICUs) and/or performed on particular groups of patients (e.g. only children, only elderly) and/or with specific underlying conditions (e.g. immunodeficiency, organ transplant). Therefore, extracting valid case fatality proportions from published risk differences for the burden of AMR project will be particularly challenging.

Based on the heterogeneity of the studies detected, we advise to avoid pooling and averaging the results based on our categorizing criteria. We suggest below a list of methods for the selection of the studies identified. This list is not mutually exclusive and we recommend using a combination of the methods below to identify the published data to include in the disease models for the burden of AMR project.

### Different Approaches

- a) Grading of Recommendations, Assessment, Development and Evaluations (GRADE); it is a widely accepted systematic and explicit approach to grading the quality of evidence and strength of recommendations. This approach was used in the WHO 2014 Antimicrobial Resistance Global Report on Surveillance. The quality of evidence was collected into four categories: very low, low, moderate and high. Most studies identified in the WHO report were observational and were graded as low and very low. Our systematic review also found a predominance of observational studies and we can easily deduce that the evidence offered by our detected studies might be similar.
- b) Sample size criteria; in every statistical and inferential approach the sample size effect is fundamental to determine if an observed value or characteristic is just a case or an evidence of a reliable and repeatable phenomenon that describes the studied population. Very often studies on antibiotic resistant infections are not based on a large population and they do not include sample size calculations. A small sample size

weakens the evidence produced by their results; the approach, therefore, would consist of including only studies that have a “large” sample size. The definition of large can be described as consistent with a sample size calculation that we can perform based on the data available in literature.

- c) Control for confounders and biases; the control for confounders and biases is another fundamental criterion in the evaluation of the evidence. The best quality studies we identified were matched case control studies with matching for the main variables of the two groups that might interfere in the disease outcome (e.g. age, underlying health conditions, therapy etc.). The final selection would include studies that control the cases and control groups by matching them for specific and defined variables or those performing statistical analysis that controls for those variables (e.g. multivariate logistic regression model). If a study seems of good quality but lacks one or two essential quality criteria (e.g. control for confounders and biases), one could contact the author/s of the study and ask for raw data. However, this approach might be very time-consuming and the outcome is uncertain.
- d) Meta-analysis; Meta-analyses of the results of all detected studies as they are reported in the articles could be possible. Another approach would entail extracting information on each single patient and their characteristics and insert them in a self-build database. However, this would require contacting authors in order to fill in the information gaps of the published studies.
- e) Self-designed evaluation grid; the previously described approaches (b-d) give us useful information on the quality and reliability of the evidence produced by a study. this information could be pooled together in a grid showing the selected criteria to be assigned to every study (we suggest those listed in b, c and d). The criteria would be qualitative ordinal variables with pre-assigned values. The grid would lead to an approach similar to the GRADE but could be tailored for studies on antibiotic resistance. The aspects to consider and their ranking should be agreed with antibiotic resistance experts.

The purpose of this summary is to list some aspects that should be considered in the evaluation of the detected studies.

Further expert’s opinions and a specific literature research can help considering the best approach and include additional aspects.

## References

1. Kim SB, Min YH, Cheong JW, et al. Incidence and risk factors for carbapenem- and multidrug-resistant *Acinetobacter baumannii* bacteremia in hematopoietic stem cell transplantation recipients. *Scandinavian journal of infectious diseases*. Feb 2014;46(2):81-88.
2. Thatrimontrichai A, Apisarnthanarak A, Chanvitan P, Janjindamai W, Dissaneevate S, Maneenil G. Risk factors and outcomes of carbapenem-resistant *Acinetobacter baumannii* bacteremia in neonatal intensive care unit: a case-case-control study. *The Pediatric infectious disease journal*. Feb 2013;32(2):140-145.
3. Deris ZZ, Shafei MN, Harun A. Risk factors and outcomes of imipenem-resistant *Acinetobacter* bloodstream infection in North-Eastern Malaysia. *Asian Pacific journal of tropical biomedicine*. Aug 2011;1(4):313-315.
4. Esterly JS, Griffith M, Qi C, Malczynski M, Postelnick MJ, Scheetz MH. Impact of carbapenem resistance and receipt of active antimicrobial therapy on clinical outcomes of *Acinetobacter baumannii* bloodstream infections. *Antimicrobial agents and chemotherapy*. Oct 2011;55(10):4844-4849.
5. Huang ST, Chiang MC, Kuo SC, et al. Risk factors and clinical outcomes of patients with carbapenem-resistant *Acinetobacter baumannii* bacteremia. *Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi*. Oct 2012;45(5):356-362.
6. Jamulitrat S, Arunpan P, Phainuphong P. Attributable mortality of imipenem-resistant nosocomial *Acinetobacter baumannii* bloodstream infection. *Journal of the Medical Association of Thailand = Chotmaihet thangphaet*. Mar 2009;92(3):413-419.
7. Kim YJ, Kim SI, Hong KW, Kim YR, Park YJ, Kang MW. Risk factors for mortality in patients with carbapenem-resistant *Acinetobacter baumannii* bacteremia: impact of appropriate antimicrobial therapy. *Journal of Korean medical science*. May 2012;27(5):471-475.
8. Kumar A, Randhawa VS, Nirupam N, Rai Y, Saili A. Risk factors for carbapenem-resistant *Acinetobacter baumannii* blood stream infections in a neonatal intensive care unit, Delhi, India. *Journal of infection in developing countries*. Aug 13 2014;8(8):1049-1054.
9. Routsis C, Pratikaki M, Platsouka E, et al. Carbapenem-resistant versus carbapenem-susceptible *Acinetobacter baumannii* bacteremia in a Greek intensive care unit: risk factors, clinical features and outcomes. *Infection*. Jun 2010;38(3):173-180.
10. Tal-Jasper R, Katz DE, Amrami N, et al. Clinical and epidemiological significance of carbapenem resistance in *Acinetobacter baumannii* infections. *Antimicrobial agents and chemotherapy*. 2016;60(5):3127-3131.
11. Thatrimontrichai A, Techato C, Dissaneevate S, et al. Risk factors and outcomes of carbapenem-resistant *Acinetobacter baumannii* ventilator-associated pneumonia in the neonate: A case-case-control study. *Journal of Infection and Chemotherapy*. 2016;22(7):444-449.
12. Chang HC, Chen YC, Lin MC, et al. Mortality risk factors in patients with *Acinetobacter baumannii* ventilator-associated pneumonia. *Journal of the Formosan Medical Association = Taiwan yi zhi*. Sep 2011;110(9):564-571.
13. Garnacho-Montero J, Ortiz-Leyba C, Jimenez-Jimenez FJ, et al. Treatment of multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia (VAP) with intravenous colistin: a comparison with imipenem-susceptible VAP. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. May 1 2003;36(9):1111-1118.

14. Zheng YL, Wan YF, Zhou LY, et al. Risk factors and mortality of patients with nosocomial carbapenem-resistant *Acinetobacter baumannii* pneumonia. *American journal of infection control*. Jul 2013;41(7):e59-63.
15. Henig O, Weber G, Hoshen MB, et al. Risk factors for and impact of carbapenem-resistant *Acinetobacter baumannii* colonization and infection: matched case-control study. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology*. Oct 2015;34(10):2063-2068.
16. Nazer LH, Kharabsheh A, Rimawi D, Mubarak S, Hawari F. Characteristics and Outcomes of *Acinetobacter baumannii* Infections in Critically Ill Patients with Cancer: A Matched Case-Control Study. *Microbial drug resistance (Larchmont, N.Y.)*. Oct 2015;21(5):556-561.
17. Aydemir H, Celebi G, Piskin N, et al. Mortality attributable to carbapenem-resistant nosocomial *Acinetobacter baumannii* infections in a Turkish university hospital. *Japanese journal of infectious diseases*. 2012;65(1):66-71.
18. de Gouvea EF, Martins IS, Halpern M, et al. The influence of carbapenem resistance on mortality in solid organ transplant recipients with *Acinetobacter baumannii* infection. *BMC infectious diseases*. Dec 13 2012;12:351.
19. del Mar Tomas M, Cartelle M, Pertega S, et al. Hospital outbreak caused by a carbapenem-resistant strain of *Acinetobacter baumannii*: patient prognosis and risk-factors for colonisation and infection. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. Jul 2005;11(7):540-546.
20. Lautenbach E, Synnestvedt M, Weiner MG, et al. Epidemiology and impact of imipenem resistance in *Acinetobacter baumannii*. *Infection control and hospital epidemiology*. Dec 2009;30(12):1186-1192.
21. Lemos EV, de la Hoz FP, Alvis N, et al. Impact of carbapenem resistance on clinical and economic outcomes among patients with *Acinetobacter baumannii* infection in Colombia. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. Feb 2014;20(2):174-180.
22. Lemos EV, de la Hoz FP, Einarson TR, et al. Carbapenem resistance and mortality in patients with *Acinetobacter baumannii* infection: systematic review and meta-analysis. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. May 2014;20(5):416-423.
23. Sheng WH, Liao CH, Lauderdale TL, et al. A multicenter study of risk factors and outcome of hospitalized patients with infections due to carbapenem-resistant *Acinetobacter baumannii*. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases*. Sep 2010;14(9):e764-769.
24. Brooklyn Antibiotic Resistance Task Force. The cost of antibiotic resistance: effect of resistance among *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* on length of hospital stay. *Infection control and hospital epidemiology*. Feb 2002;23(2):106-108.
25. Wang YC, Lee YT, Yang YS, et al. Risk factors and outcome for colistin-resistant *Acinetobacter nosocomialis* bacteraemia in patients without previous colistin exposure. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. Aug 2015;21(8):758-764.
26. Taneja N, Singh G, Singh M, Sharma M. Emergence of tigecycline & colistin resistant *Acinetobacter baumannii* in patients with complicated urinary tract infections in north India. *Indian J Med Res*. Jun 2011;133:681-684.
27. Baran I, Mumcuoglu I, Aksu N, et al. Evaluation of colistin-resistant *Acinetobacter* strains. *Clinical Microbiology and Infection*. 2012;18:321.



28. Kontopidou F, Plachouras D, Papadomichelakis E, et al. Colonization and infection by colistin-resistant Gram-negative bacteria in a cohort of critically ill patients. *Clinical Microbiology and Infection*. 2011;17(11):E9-E11.
29. Lee SY, Shin JH, Park KH, et al. Identification, genotypic relation, and clinical features of colistin-resistant isolates of Acinetobacter genomic species 13BJ/14TU from bloodstreams of patients in a university hospital. *Journal of Clinical Microbiology*. 2014;52(3):931-939.
30. Qureshi ZA, Hittle LE, O'Hara JA, et al. Colistin-resistant acinetobacter baumannii: Beyond carbapenem resistance. *Clinical Infectious Diseases*. 2015;60(9):1295-1303.
31. Al Jarousha AM, El Jadba AH, Al Afifi AS, El Qouqa IA. Nosocomial multidrug-resistant Acinetobacter baumannii in the neonatal intensive care unit in Gaza City, Palestine. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases*. Sep 2009;13(5):623-628.
32. Gulen TA, Guner R, Celikbilek N, Keske S, Tasyaran M. Clinical importance and cost of bacteremia caused by nosocomial multi drug resistant acinetobacter baumannii. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases*. Sep 2015;38:32-35.
33. Anunnatsiri S, Tonsawan P. Risk factors and clinical outcomes of multidrug-resistant Acinetobacter baumannii bacteremia at a university hospital in Thailand. *The Southeast Asian journal of tropical medicine and public health*. May 2011;42(3):693-703.
34. Fitzpatrick MA, Ozer E, Bolon MK, Hauser AR. Influence of ACB complex genospecies on clinical outcomes in a U.S. hospital with high rates of multidrug resistance. *The Journal of infection*. Feb 2015;70(2):144-152.
35. Guo N, Xue W, Tang D, Ding J, Zhao B. Risk factors and outcomes of hospitalized patients with blood infections caused by multidrug-resistant Acinetobacter baumannii complex in a hospital of Northern China. *American journal of infection control*. 2016;44(4):e37-e39.
36. Lee NY, Lee HC, Ko NY, et al. Clinical and economic impact of multidrug resistance in nosocomial Acinetobacter baumannii bacteremia. *Infection control and hospital epidemiology*. Jun 2007;28(6):713-719.
37. Lee NY, Chang TC, Wu CJ, et al. Clinical manifestations, antimicrobial therapy, and prognostic factors of monomicrobial Acinetobacter baumannii complex bacteremia. *The Journal of infection*. Sep 2010;61(3):219-227.
38. Smolyakov R, Borer A, Riesenberk K, et al. Nosocomial multi-drug resistant Acinetobacter baumannii bloodstream infection: risk factors and outcome with ampicillin-sulbactam treatment. *The Journal of hospital infection*. May 2003;54(1):32-38.
39. Cai XF, Sun JM, Bao LS, Li WB. Risk factors and antibiotic resistance of pneumonia caused by multidrug resistant Acinetobacter baumannii in pediatric intensive care unit. *World Journal of Emergency Medicine*. 2012;3(3):202-207.
40. Inchai J, Pothirat C, Bumroongkit C, Limsukon A, Khositsakulchai W, Liwsrisakun C. Prognostic factors associated with mortality of drug-resistant Acinetobacter baumannii ventilator-associated pneumonia. *Journal of Intensive Care*. 2015;3(1).
41. Park II, Kim IK, Koo HC, et al. Clinical characteristics and prognosis of Acinetobacter nosocomial pneumonia between MDR and non-MDR. *Tuberculosis and Respiratory Diseases*. 2006;61(1):13-19.
42. Abbo A, Carmeli Y, Navon-Venezia S, Siegman-Igra Y, Schwaber MJ. Impact of multi-drug-resistant Acinetobacter baumannii on clinical outcomes. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology*. Nov 2007;26(11):793-800.

43. Fukuta Y, Doi Y, Muder RR, et al. Risk factors for acquisition of multi-drug resistant *Acinetobacter baumannii* among cancer patients. *International Journal of Antimicrobial Agents*. 2013;42:S140-S141.
44. Lee H, Lee H. Clinical and economic evaluation of multidrug-resistant *Acinetobacter baumannii* colonization in the intensive care unit. *Infection and Chemotherapy*. 2016;48(3):174-180.
45. Brahmi N, Beji O, Abidi N, et al. Epidemiology and risk factors for colonization and infection by *Acinetobacter baumannii* in an ICU in Tunisia, where this pathogen is endemic. *Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy*. Dec 2007;13(6):400-404.
46. Daniels TL, Deppen S, Arbogast PG, Griffin MR, Schaffner W, Talbot TR. Mortality rates associated with multidrug-resistant *Acinetobacter baumannii* infection in surgical intensive care units. *Infection control and hospital epidemiology*. Nov 2008;29(11):1080-1083.
47. Lemos EV, De la Hoz Restrepo F, Alvis N, Quevedo E, Canon O, Leon Y. [*Acinetobacter baumannii* - related mortality in intensive care units in Colombia]. *Revista panamericana de salud publica = Pan American journal of public health*. Oct 2011;30(4):287-294.
48. Pierri MD, Crescenzi G, Capestro F, et al. Risk Factors and Impact on Clinical Outcome of Multidrug-Resistant *Acinetobacter Baumannii* Acquisition in Cardiac Surgery Patients. *Journal of Cardiothoracic and Vascular Anesthesia*. 2016;30(3):680-686.
49. Zilberberg MD, Nathanson BH, Sulham K, Fan W, Shorr AF. Multidrug resistance, inappropriate empiric therapy, and hospital mortality in *Acinetobacter baumannii* pneumonia and sepsis. *Critical Care*. 2016;20(1).
50. Lambert ML, Suetens C, Savey A, et al. Clinical outcomes of health-care-associated infections and antimicrobial resistance in patients admitted to European intensive-care units: A cohort study. *The Lancet Infectious Diseases*. 2011;11(1):30-38.
51. Chang HJ, Hsu PC, Yang CC, et al. Risk factors and outcomes of carbapenem-nonsusceptible *Escherichia coli* bacteremia: A matched case-control study. *Journal of Microbiology, Immunology and Infection*. 2011;44(2):125-130.
52. Epstein L, Hunter JC, Arwady MA, et al. New Delhi metallo- $\beta$ -lactamase-producing carbapenem-resistant *Escherichia coli* associated with exposure to duodenoscopes. *JAMA - Journal of the American Medical Association*. 2014;312(14):1447-1455.
53. Ahn JY, Song JE, Kim MH, et al. Risk factors for the acquisition of carbapenem-resistant *Escherichia coli* at a tertiary care center in South Korea: A matched case-control study. *American journal of infection control*. 2014;42(6):621-625.
54. Balkan, II, Aygun G, Aydin S, et al. Blood stream infections due to OXA-48-like carbapenemase-producing Enterobacteriaceae: treatment and survival. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases*. Sep 2014;26:51-56.
55. Poirel L, Savov E, Nazli A, et al. Outbreak caused by NDM-1- and RmtB-producing *Escherichia coli* in Bulgaria. *Antimicrobial agents and chemotherapy*. 2014;58(4):2472-2474.
56. Porwal R, Gopalakrishnan R, Rajesh NJ, Ramasubramanian V. Carbapenem resistant Gram-negative bacteremia in an Indian intensive care unit: A review of the clinical profile and treatment outcome of 50 patients. *Indian Journal of Critical Care Medicine*. 2014;18(11):750-753.
57. Shukla N, Tulasigeri C, Kate A, et al. High carbapenem resistance in gram negative bacterial isolates: An outcome study. *American Journal of Respiratory and Critical Care Medicine*. 2013;187.

58. Liu YY, Wang Y, Walsh TR, et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. *The Lancet. Infectious diseases*. Feb 2016;16(2):161-168.
59. Nordmann P, Lienhard R, Kieffer N, Clerc O, Poirel L. Plasmid-mediated colistin-resistant *Escherichia coli* in bacteremia in Switzerland. *Clinical Infectious Diseases*. 2016;62(10):1322-1323.
60. Oostdijk EA, Leverstein-van Hall M, Muilwijk J, Kesecioglu J, Bonten MJ. Colistin resistance in Gram-negative bacteria during prophylactic colistin use in intensive care units. *Clinical Microbiology and Infection*. 2011;17:S294.
61. de Kraker MEA, Wolkewitz M, Davey PG, et al. Burden of antimicrobial resistance in European hospitals: Excess mortality and length of hospital stay associated with bloodstream infections due to *Escherichia coli* resistant to third-generation cephalosporins. *Journal of Antimicrobial Chemotherapy*. 2011;66(2):398-407.
62. Anunnatsiri S, Towiwat P, Chaimanee P. Risk factors and clinical outcomes of extended spectrum beta-lactamase (ESBL)-producing *Escherichia coli* septicemia at Srinagarind University Hospital, Thailand. *The Southeast Asian journal of tropical medicine and public health*. Sep 2012;43(5):1169-1177.
63. Apisarnthanarak A, Kiratisin P, Mundy LM. Predictors of mortality from community-onset bloodstream infections due to extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*. *Infection control and hospital epidemiology*. Jul 2008;29(7):671-674.
64. Cornejo-Juarez P, Perez-Jimenez C, Silva-Sanchez J, et al. Molecular analysis and risk factors for *Escherichia coli* producing extended-spectrum beta-lactamase bloodstream infection in hematological malignancies. *PloS one*. 2012;7(4):e35780.
65. Courpon-Claudinon A, Lefort A, Panhard X, et al. Bacteraemia caused by third-generation cephalosporin-resistant *Escherichia coli* in France: Prevalence, molecular epidemiology and clinical features. *Clinical Microbiology and Infection*. 2011;17(4):557-565.
66. Ortega M, Marco F, Soriano A, et al. Analysis of 4758 *Escherichia coli* bacteraemia episodes: predictive factors for isolation of an antibiotic-resistant strain and their impact on the outcome. *The Journal of antimicrobial chemotherapy*. Mar 2009;63(3):568-574.
67. Treccarichi EM, Tumbarello M, Spanu T, et al. Incidence and clinical impact of extended-spectrum-beta-lactamase (ESBL) production and fluoroquinolone resistance in bloodstream infections caused by *Escherichia coli* in patients with hematological malignancies. *The Journal of infection*. Apr 2009;58(4):299-307.
68. Hsieh CJ, Shen YH, Hwang KP. Clinical implications, risk factors and mortality following community-onset bacteremia caused by extended-spectrum beta-lactamase (ESBL) and non-ESBL producing *Escherichia coli*. *Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi*. Jun 2010;43(3):240-248.
69. Tumbarello M, Spanu T, Di Bidino R, et al. Costs of bloodstream infections caused by *Escherichia coli* and influence of extended-spectrum-beta-lactamase production and inadequate initial antibiotic therapy. *Antimicrobial agents and chemotherapy*. Oct 2010;54(10):4085-4091.
70. Gudiol C, Calatayud L, Garcia-Vidal C, et al. Bacteraemia due to extended-spectrum beta-lactamase-producing *Escherichia coli* (ESBL-EC) in cancer patients: clinical features, risk factors, molecular epidemiology and outcome. *The Journal of antimicrobial chemotherapy*. Feb 2010;65(2):333-341.
71. Ho PL, Chan WM, Tsang KW, Wong SS, Young K. Bacteremia caused by *Escherichia coli* producing extended-spectrum beta-lactamase: a case-control study of risk factors and outcomes. *Scandinavian journal of infectious diseases*. 2002;34(8):567-573.

72. Rodriguez-Bano J, Picon E, Gijon P, et al. Community-onset bacteremia due to extended-spectrum beta-lactamase-producing *Escherichia coli*: risk factors and prognosis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Jan 1 2010;50(1):40-48.
73. Kang CI, Song JH, Chung DR, et al. Risk factors and treatment outcomes of community-onset bacteraemia caused by extended-spectrum beta-lactamase-producing *Escherichia coli*. *Int J Antimicrob Agents*. Sep 2010;36(3):284-287.
74. Garcia Hernandez A, Garcia-Vazquez E, Gomez Gomez J, Canteras M, Hernandez-Torres A, Ruiz Gomez J. [Predictive factors of ESBL versus non-ESBL *Escherichia coli* bacteraemia and influence of resistance on the mortality of the patients]. *Medicina clinica*. Jan 29 2011;136(2):56-60.
75. Denis B, Lafaurie M, Donay JL, et al. Prevalence, risk factors, and impact on clinical outcome of extended-spectrum beta-lactamase-producing *Escherichia coli* bacteraemia: a five-year study. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases*. Oct 2015;39:1-6.
76. Ha YE, Kang CI, Cha MK, et al. Epidemiology and clinical outcomes of bloodstream infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli* in patients with cancer. *Int J Antimicrob Agents*. Nov 2013;42(5):403-409.
77. Kaya O, Akcam FZ, Gonen I, Unal O, Ceylan T. Risk factors for bacteremia due to extended-spectrum beta-lactamase-producing *Escherichia coli* in a Turkish hospital. *Journal of infection in developing countries*. Jul 15 2013;7(7):507-512.
78. Kim SH, Kwon JC, Choi SM, et al. *Escherichia coli* and *Klebsiella pneumoniae* bacteremia in patients with neutropenic fever: factors associated with extended-spectrum beta-lactamase production and its impact on outcome. *Annals of hematology*. Apr 2013;92(4):533-541.
79. Leistner R, Gurntke S, Sakellariou C, et al. Bloodstream infection due to extended-spectrum beta-lactamase (ESBL)-positive *K. pneumoniae* and *E. coli*: an analysis of the disease burden in a large cohort. *Infection*. Dec 2014;42(6):991-997.
80. Leistner R, Sakellariou C, Gurntke S, et al. Mortality and molecular epidemiology associated with extended-spectrum  $\beta$ -lactamase production in *Escherichia coli* from bloodstream infection. *Infection and Drug Resistance*. 2014;7:57-62.
81. Martelius T, Jalava J, Karki T, Mottonen T, Ollgren J, Lyytikainen O. Nosocomial bloodstream infections caused by *Escherichia coli* and *Klebsiella pneumoniae* resistant to third-generation cephalosporins, Finland, 1999-2013: Trends, patient characteristics and mortality. *Infectious diseases (London, England)*. 2016;48(3):229-234.
82. Park SH, Choi SM, Lee DG, et al. Emergence of extended-spectrum beta-lactamase-producing *Escherichia coli* as a cause of community-onset bacteremia in South Korea: risk factors and clinical outcomes. *Microbial drug resistance (Larchmont, N.Y.)*. Dec 2011;17(4):537-544.
83. Yip T, Tse KC, Lam MF, et al. Risk factors and outcomes of extended-spectrum beta-lactamase-producing *E. coli* peritonitis in CAPD patients. *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis*. Mar-Apr 2006;26(2):191-197.
84. Van Aken S, Lund N, Ahl J, Odenholt I, Tham J. Risk factors, outcome and impact of empirical antimicrobial treatment in extended-spectrum beta-lactamase-producing *Escherichia coli* bacteraemia. *Scandinavian journal of infectious diseases*. Nov 2014;46(11):753-762.
85. Melzer M, Petersen I. Mortality following bacteraemic infection caused by extended spectrum beta-lactamase (ESBL) producing *E. coli* compared to non-ESBL producing *E. coli*. *The Journal of infection*. Sep 2007;55(3):254-259.

86. Al-Otaibi FE, Bukhari EE. Clinical and laboratory profiles of urinary tract infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli* in a tertiary care center in central Saudi Arabia. *Saudi medical journal*. Feb 2013;34(2):171-176.
87. Ena J, Arjona F, Martinez-Peinado C, Lopez-Perezagua Mdel M, Amador C. Epidemiology of urinary tract infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli*. *Urology*. Dec 2006;68(6):1169-1174.
88. Suankratay C, Jutivorakool K, Jirajariyavej S. A prospective study of ceftriaxone treatment in acute pyelonephritis caused by extended-spectrum beta-lactamase-producing bacteria. *Journal of the Medical Association of Thailand = Chotmaihet thangphaet*. Aug 2008;91(8):1172-1181.
89. Esteve-Palau E, Solande G, Sanchez F, et al. Clinical and economic impact of urinary tract infections caused by ESBL-producing *Escherichia coli* requiring hospitalization: A matched cohort study. *The Journal of infection*. Dec 2015;71(6):667-674.
90. Park SH, Choi SM, Lee DG, et al. Impact of extended-spectrum beta-lactamase production on treatment outcomes of acute pyelonephritis caused by *Escherichia coli* in patients without health care-associated risk factors. *Antimicrobial agents and chemotherapy*. Apr 2015;59(4):1962-1968.
91. Arnan M, Gudiol C, Calatayud L, et al. Risk factors for, and clinical relevance of, faecal extended-spectrum beta-lactamase producing *Escherichia coli* (ESBL-EC) carriage in neutropenic patients with haematological malignancies. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology*. Mar 2011;30(3):355-360.
92. Nicolas-Chanoine MH, Jarlier V, Robert J, et al. Patient's origin and lifestyle associated with CTX-M-producing *Escherichia coli*: a case-control-control study. *PloS one*. 2012;7(1):e30498.
93. Hayakawa K, Gattu S, Marchaim D, et al. Epidemiology and risk factors for isolation of *Escherichia coli* producing CTX-M-type extended-spectrum beta-lactamase in a large U.S. Medical Center. *Antimicrobial agents and chemotherapy*. Aug 2013;57(8):4010-4018.
94. Pena C, Gudiol C, Calatayud L, et al. Infections due to *Escherichia coli* producing extended-spectrum beta-lactamase among hospitalised patients: factors influencing mortality. *The Journal of hospital infection*. Feb 2008;68(2):116-122.
95. Kang CI, Wi YM, Lee MY, et al. Epidemiology and risk factors of community onset infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli* strains. *J Clin Microbiol*. Feb 2012;50(2):312-317.
96. Maslikowska JA, Walker SAN, Elligsen M, et al. Impact of infection with extended-spectrum  $\beta$ -lactamase-producing *Escherichia coli* or *Klebsiella* species on outcome and hospitalization costs. *Journal of Hospital Infection*. 2016;92(1):33-41.
97. Falagas ME, Tansarli GS, Karageorgopoulos DE, Vardakas KZ. Deaths attributable to carbapenem-resistant Enterobacteriaceae infections. *Emerging infectious diseases*. Jul 2014;20(7):1170-1175.
98. Viale P, Giannella M, Lewis R, Trecarichi EM, Petrosillo N, Tumbarello M. Predictors of mortality in multidrug-resistant *Klebsiella pneumoniae* bloodstream infections. *Expert Review of Anti-Infective Therapy*. 2013;11(10):1053-1063.
99. Boyle DP, Zembower TR. Epidemiology and Management of Emerging Drug-Resistant Gram-Negative Bacteria: Extended-Spectrum beta-Lactamases and Beyond. *The Urologic clinics of North America*. Nov 2015;42(4):493-505.
100. Borer A, Saidel-Odes L, Riesenberk K, et al. Attributable mortality rate for carbapenem-resistant *Klebsiella pneumoniae* bacteremia. *Infection control and hospital epidemiology*. 2009;30(10):972-976.

101. Gallagher JC, Kuriakose S, Haynes K, Axelrod P. Case-case-control study of patients with carbapenem-resistant and third-generation-cephalosporin-resistant *Klebsiella pneumoniae* bloodstream infections. *Antimicrobial agents and chemotherapy*. Oct 2014;58(10):5732-5735.
102. Mouloudi E, Massa E, Papadopoulos S, et al. Bloodstream infections caused by carbapenemase-producing *Klebsiella pneumoniae* among intensive care unit patients after orthotopic liver transplantation: Risk factors for infection and impact of resistance on outcomes. *Transplantation Proceedings*. 2014;46(9):3216-3218.
103. Mouloudi E, Protonotariou E, Zagorianou A, et al. Bloodstream infections caused by metallo-beta-lactamase/*Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* among intensive care unit patients in Greece: risk factors for infection and impact of type of resistance on outcomes. *Infection control and hospital epidemiology*. Dec 2010;31(12):1250-1256.
104. Simkins J, Muggia V, Cohen HW, Minamoto GY. Carbapenem-resistant *Klebsiella pneumoniae* infections in kidney transplant recipients: A case-control study. *Transplant Infectious Disease*. 2014;16(5):775-782.
105. Hussein K, Raz-Pasteur A, Finkelstein R, et al. Impact of carbapenem resistance on the outcome of patients' hospital-acquired bacteraemia caused by *Klebsiella pneumoniae*. *Journal of Hospital Infection*. 2013;83(4):307-313.
106. Ben-David D, Kordevani R, Keller N, et al. Outcome of carbapenem resistant *Klebsiella pneumoniae* bloodstream infections. *Clinical Microbiology and Infection*. 2012;18(1):54-60.
107. Daikos GL, Petrikos P, Psychogiou M, et al. Prospective observational study of the impact of VIM-1 metallo-beta-lactamase on the outcome of patients with *Klebsiella pneumoniae* bloodstream infections. *Antimicrobial agents and chemotherapy*. May 2009;53(5):1868-1873.
108. Brizendine KD, Richter SS, Cober ED, Van Duin D. Carbapenem-resistant *Klebsiella pneumoniae* urinary tract infection following solid organ transplantation. *Antimicrobial agents and chemotherapy*. 2015;59(1):553-557.
109. Pouch SM, Kubin CJ, Satlin MJ, et al. Epidemiology and outcomes of carbapenem-resistant *Klebsiella pneumoniae* bacteriuria in kidney transplant recipients. *Transplant Infectious Disease*. 2015;17(6):800-809.
110. Shilo S, Assous MV, Lachish T, et al. Risk factors for bacteriuria with carbapenem-resistant *Klebsiella pneumoniae* and its impact on mortality: A case-control study. *Infection*. 2013;41(2):503-509.
111. Giannella M, Morelli MC, Cristini F, et al. Carbapenem-resistant *Klebsiella pneumoniae* colonization at liver transplantation: a management challenge. *Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society*. May 2014;20(5):631-633.
112. Lubbert C, Becker-Rux D, Rodloff AC, et al. Colonization of liver transplant recipients with KPC-producing *Klebsiella pneumoniae* is associated with high infection rates and excess mortality: a case-control analysis. *Infection*. Apr 2014;42(2):309-316.
113. Nouvenne A, Ticinesi A, Lauretani F, et al. Comorbidities and disease severity as risk factors for carbapenem-resistant *Klebsiella pneumoniae* colonization: report of an experience in an internal medicine unit. *PloS one*. 2014;9(10):e110001.
114. Bleumin D, Cohen MJ, Moranne O, et al. Carbapenem-resistant *Klebsiella pneumoniae* is associated with poor outcome in hemodialysis patients. *The Journal of infection*. Oct 2012;65(4):318-325.

115. Debby BD, Ganor O, Yasmin M, et al. Epidemiology of carbapenem resistant *Klebsiella pneumoniae* colonization in an intensive care unit. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology*. Aug 2012;31(8):1811-1817.
116. Schwaber MJ, Klarfeld-Lidji S, Navon-Venezia S, Schwartz D, Leavitt A, Carmeli Y. Predictors of carbapenem-resistant *Klebsiella pneumoniae* acquisition among hospitalized adults and effect of acquisition on mortality. *Antimicrobial agents and chemotherapy*. Mar 2008;52(3):1028-1033.
117. Pereira MR, Scully BF, Pouch SM, et al. Risk factors and outcomes of carbapenem-resistant *Klebsiella pneumoniae* infections in liver transplant recipients. *Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society*. Dec 2015;21(12):1511-1519.
118. Kofteridis DP, Valachis A, Dimopoulou D, et al. Risk factors for carbapenem-resistant *Klebsiella pneumoniae* infection/colonization: a case-case-control study. *Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy*. May 2014;20(5):293-297.
119. Candevir Ulu A, Kurtaran B, Inal AS, et al. Risk factors of carbapenem-resistant *Klebsiella pneumoniae* infection: a serious threat in ICUs. *Medical science monitor : international medical journal of experimental and clinical research*. 2015;21:219-224.
120. Dizbay M, Guzel Tunccan O, Karasahin O, Aktas F. Emergence of carbapenem-resistant *Klebsiella* spp. infections in a Turkish university hospital: epidemiology and risk factors. *Journal of infection in developing countries*. Jan 2014;8(1):44-49.
121. Hoxha A, Karki T, Giambi C, et al. Attributable mortality of carbapenem-resistant *Klebsiella pneumoniae* infections in a prospective matched cohort study in Italy, 2012-2013. *The Journal of hospital infection*. Jan 2016;92(1):61-66.
122. Jiao Y, Qin Y, Liu J, et al. Risk factors for carbapenem-resistant *Klebsiella pneumoniae* infection/colonization and predictors of mortality: a retrospective study. *Pathogens and global health*. Mar 2015;109(2):68-74.
123. Patel G, Huprikar S, Factor SH, Jenkins SG, Calfee DP. Outcomes of carbapenem-resistant *Klebsiella pneumoniae* infection and the impact of antimicrobial and adjunctive therapies. *Infection control and hospital epidemiology*. Dec 2008;29(12):1099-1106.
124. Correa L, Martino MD, Siqueira I, et al. A hospital-based matched case-control study to identify clinical outcome and risk factors associated with carbapenem-resistant *Klebsiella pneumoniae* infection. *BMC infectious diseases*. 2013;13:80.
125. Centers for Disease Control and Prevention C. *Carbapenem-Resistant Klebsiella pneumoniae Associated with a Long-Term--Care Facility--West Virginia, 2009-2011* October 21 2011.
126. Falagas ME, Rafailidis PI, Kofteridis D, et al. Risk factors of carbapenem-resistant *Klebsiella pneumoniae* infections: a matched case control study. *The Journal of antimicrobial chemotherapy*. Nov 2007;60(5):1124-1130.
127. Hauck C, Cober E, Richter SS, et al. Spectrum of excess mortality due to carbapenem-resistant *Klebsiella pneumoniae* infections. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. Jun 2016;22(6):513-519.
128. Atmaca O, Zarakolu P, Karahan C, Cakir B, Unal S. [Risk factors and antibiotic use in methicillin-resistant *Staphylococcus aureus* bacteremia in hospitalized patients at Hacettepe University Adult and Oncology Hospitals (2004-2011) and antimicrobial susceptibilities of the isolates: a nested case-control study]. *Mikrobiyoloji bulteni*. Oct 2014;48(4):523-537.

129. Daikos GL, Karabinis A, Paramythiotou E, et al. VIM-1-producing *Klebsiella pneumoniae* bloodstream infections: analysis of 28 cases. *Int J Antimicrob Agents*. Apr 2007;29(4):471-473.
130. Lee NY, Wu JJ, Lin SH, Ko WC, Tsai LH, Yan JJ. Characterization of carbapenem-nonsusceptible *Klebsiella pneumoniae* bloodstream isolates at a Taiwanese hospital: clinical impacts of lowered breakpoints for carbapenems. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology*. Aug 2012;31(8):1941-1950.
131. Marchaim D, Chopra T, Pogue JM, et al. Outbreak of colistin-resistant, carbapenem-resistant *Klebsiella pneumoniae* in metropolitan Detroit, Michigan. *Antimicrobial agents and chemotherapy*. Feb 2011;55(2):593-599.
132. Zarkotou O, Pournaras S, Voulgari E, et al. Risk factors and outcomes associated with acquisition of colistin-resistant KPC-producing *Klebsiella pneumoniae*: a matched case-control study. *J Clin Microbiol*. Jun 2010;48(6):2271-2274.
133. Capone A, Giannella M, Fortini D, et al. High rate of colistin resistance among patients with carbapenem-resistant *Klebsiella pneumoniae* infection accounts for an excess of mortality. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. Jan 2013;19(1):E23-30.
134. Rojas LJ, Salim M, Cober E, et al. Colistin Resistance in Carbapenem-Resistant *Klebsiella pneumoniae*: Laboratory Detection and Impact on Mortality. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Dec 10 2016.
135. Falagas ME, Rafailidis PI, Matthaïou DK, Virtzili S, Nikita D, Michalopoulos A. Pandrug-resistant *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* infections: characteristics and outcome in a series of 28 patients. *Int J Antimicrob Agents*. Nov 2008;32(5):450-454.
136. Falagas ME, Bliziotis IA, Kasiakou SK, Samonis G, Athanassopoulou P, Michalopoulos A. Outcome of infections due to pandrug-resistant (PDR) Gram-negative bacteria. *BMC infectious diseases*. Apr 08 2005;5:24.
137. Antoniadou A, Kontopidou F, Poulakou G, et al. Colistin-resistant isolates of *Klebsiella pneumoniae* emerging in intensive care unit patients: first report of a multiclonal cluster. *The Journal of antimicrobial chemotherapy*. Apr 2007;59(4):786-790.
138. Toth A, Damjanova I, Puskas E, et al. Emergence of a colistin-resistant KPC-2-producing *Klebsiella pneumoniae* ST258 clone in Hungary. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology*. Jul 2010;29(7):765-769.
139. Kontopoulou K, Protonotariou E, Vasilakos K, et al. Hospital outbreak caused by *Klebsiella pneumoniae* producing KPC-2 beta-lactamase resistant to colistin. *The Journal of hospital infection*. Sep 2010;76(1):70-73.
140. Ah YM, Kim AJ, Lee JY. Colistin resistance in *Klebsiella pneumoniae*. *Int J Antimicrob Agents*. Jul 2014;44(1):8-15.
141. Gallagher JC, Kuriakose S, Haynes K, Axelrod P. Case-case-control study of patients with carbapenem-resistant and third-generation-cephalosporin-resistant *Klebsiella pneumoniae* bloodstream infections. *Antimicrob. Agents Chemother*. 2014;58(10):5732-5735.
142. Panhotra BR, Saxena AK, Al-Ghamdi AM. Extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* hospital acquired bacteremia. Risk factors and clinical outcome. *Saudi medical journal*. Dec 2004;25(12):1871-1876.
143. Tumbarello M, Spanu T, Sanguinetti M, et al. Bloodstream infections caused by extended-spectrum-beta-lactamase-producing *Klebsiella pneumoniae*: risk factors, molecular



- epidemiology, and clinical outcome. *Antimicrobial agents and chemotherapy*. Feb 2006;50(2):498-504.
144. Marra AR, Wey SB, Castelo A, et al. Nosocomial bloodstream infections caused by *Klebsiella pneumoniae*: impact of extended-spectrum beta-lactamase (ESBL) production on clinical outcome in a hospital with high ESBL prevalence. *BMC infectious diseases*. 2006;6:24.
  145. Kang CI, Kim SH, Park WB, et al. Clinical outcome of bacteremic spontaneous bacterial peritonitis due to extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*. *The Korean journal of internal medicine*. Sep 2004;19(3):160-164.
  146. Kim BN, Woo JH, Kim MN, Ryu J, Kim YS. Clinical implications of extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* bacteraemia. *The Journal of hospital infection*. Oct 2002;52(2):99-106.
  147. Ariffin H, Navaratnam P, Mohamed M, et al. Ceftazidime-resistant *Klebsiella pneumoniae* bloodstream infection in children with febrile neutropenia. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases*. 2000;4(1):21-25.
  148. Mosqueda-Gomez JL, Montano-Loza A, Rolon AL, et al. Molecular epidemiology and risk factors of bloodstream infections caused by extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* A case-control study. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases*. Nov 2008;12(6):653-659.
  149. Szilagyi E, Fuzi M, Borocz K, Kurcz A, Toth A, Nagy K. Risk factors and outcomes for bloodstream infections with extended-spectrum beta -lactamase-producing *Klebsiella pneumoniae* ; Findings of the nosocomial surveillance system in Hungary. *Acta microbiologica et immunologica Hungarica*. Sep 2009;56(3):251-262.
  150. Pena C, Pujol M, Ardanuy C, et al. An outbreak of hospital-acquired *Klebsiella pneumoniae* bacteraemia, including strains producing extended-spectrum beta-lactamase. *The Journal of hospital infection*. Jan 2001;47(1):53-59.
  151. Paterson DL, Ko WC, Von Gottberg A, et al. International prospective study of *Klebsiella pneumoniae* bacteremia: implications of extended-spectrum beta-lactamase production in nosocomial Infections. *Annals of internal medicine*. Jan 6 2004;140(1):26-32.
  152. Tuon FF, Kruger M, Terreri M, Penteado-Filho SR, Gortz L. *Klebsiella* ESBL bacteremia-mortality and risk factors. *The Brazilian journal of infectious diseases : an official publication of the Brazilian Society of Infectious Diseases*. Nov-Dec 2011;15(6):594-598.
  153. Lee JA, Kang CI, Joo EJ, et al. Epidemiology and clinical features of community-onset bacteremia caused by extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae*. *Microbial drug resistance (Larchmont, N.Y.)*. Jun 2011;17(2):267-273.
  154. Brizendine KD, Richter SS, Cober ED, van Duin D. Carbapenem-resistant *Klebsiella pneumoniae* urinary tract infection following solid organ transplantation. *Antimicrobial agents and chemotherapy*. Jan 2015;59(1):553-557.
  155. Loh LC, Nor Izran Hanim Bt Abdul S, Rosdara Masayuni Bt Mohd S, Raman S, Thayaparan T, Kumar S. Hospital Outcomes of Adult Respiratory Tract Infections with Extended-Spectrum B-Lactamase (ESBL) Producing *Klebsiella Pneumoniae*. *The Malaysian journal of medical sciences : MJMS*. Jul 2007;14(2):36-40.
  156. Gomes CC, Vormittag E, Santos CR, Levin AS. Nosocomial infection with cephalosporin-resistant *Klebsiella pneumoniae* is not associated with increased mortality. *Infection control and hospital epidemiology*. Sep 2006;27(9):907-912.

157. Lin MF, Huang ML, Lai SH. Risk factors in the acquisition of extended-spectrum beta-lactamase *Klebsiella pneumoniae*: a case-control study in a district teaching hospital in Taiwan. *The Journal of hospital infection*. Jan 2003;53(1):39-45.
158. Kuo KC, Shen YH, Hwang KP. Clinical implications and risk factors of extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* infection in children: a case-control retrospective study in a medical center in southern Taiwan. *Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi*. Jun 2007;40(3):248-254.
159. Chiu S, Huang YC, Lien RI, Chou YH, Lin TY. Clinical features of nosocomial infections by extended-spectrum beta-lactamase-producing Enterobacteriaceae in neonatal intensive care units. *Acta paediatrica*. Nov 2005;94(11):1644-1649.
160. Huang Y, Zhuang S, Du M. Risk factors of nosocomial infection with extended-spectrum beta-lactamase-producing bacteria in a neonatal intensive care unit in China. *Infection*. Oct 2007;35(5):339-345.
161. Stewardson AJ, Allignol A, Beyersmann J, et al. The health and economic burden of bloodstream infections caused by antimicrobial-susceptible and non-susceptible Enterobacteriaceae and *Staphylococcus aureus* in European hospitals, 2010 and 2011: A multicentre retrospective cohort study. *Eurosurveillance*. 2016;21(33).
162. WHO. *Antimicrobial resistance: global report on surveillance*. France: WHO;2014.
163. Kuint J, Barzilai A, Regev-Yochay G, Rubinstein E, Keller N, Maayan-Metzger A. Comparison of community-acquired methicillin-resistant *Staphylococcus aureus* bacteremia to other staphylococcal species in a neonatal intensive care unit. *Eur J Pediatr*. Apr 2007;166(4):319-325.
164. Guilarde AO, Turchi MD, Martelli CM, Primo MG. *Staphylococcus aureus* bacteraemia: incidence, risk factors and predictors for death in a Brazilian teaching hospital. *The Journal of hospital infection*. Jul 2006;63(3):330-336.
165. Castillo JS, Leal AL, Cortes JA, et al. Mortality among critically ill patients with methicillin-resistant *Staphylococcus aureus* bacteremia: a multicenter cohort study in Colombia. *Revista panamericana de salud publica = Pan American journal of public health*. Nov 2012;32(5):343-350.
166. Lawes T, Edwards B, Lopez-Lozano JM, Gould I. Trends in *Staphylococcus aureus* bacteraemia and impacts of infection control practices including universal MRSA admission screening in a hospital in Scotland, 2006-2010: retrospective cohort study and time-series intervention analysis. *BMJ Open*. 2012;2(3).
167. Blot SI, Vandewoude KH, Hoste EA, Colardyn FA. Outcome and attributable mortality in critically ill patients with bacteremia involving methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*. *Arch Intern Med*. Oct 28 2002;162(19):2229-2235.
168. Talon D, Woronoff-Lemsi MC, Limat S, et al. The impact of resistance to methicillin in *Staphylococcus aureus* bacteremia on mortality. *Eur J Intern Med*. Feb 2002;13(1):31-36.
169. Soriano A, Martinez JA, Mensa J, et al. Pathogenic significance of methicillin resistance for patients with *Staphylococcus aureus* bacteremia. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Feb 2000;30(2):368-373.
170. Selvey LA, Whitby M, Johnson B. Nosocomial methicillin-resistant *Staphylococcus aureus* bacteremia: is it any worse than nosocomial methicillin-sensitive *Staphylococcus aureus* bacteremia? *Infection control and hospital epidemiology*. Oct 2000;21(10):645-648.
171. Rubio-Terres C, Garau J, Grau S, Martinez-Martinez L, Cast of Resistance Study g. Cost of bacteraemia caused by methicillin-resistant vs. methicillin-susceptible *Staphylococcus aureus* in Spain: a retrospective cohort study. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. Jun 2010;16(6):722-728.

172. Romero-Vivas J, Rubio M, Fernandez C, Picazo JJ. Mortality associated with nosocomial bacteremia due to methicillin-resistant *Staphylococcus aureus*. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Dec 1995;21(6):1417-1423.
173. Reshad K, Tanaka F, Sekine T, et al. [A prospective study of septic episodes due to *Staphylococcus aureus* and the background of the patients]. *Kansenshogaku Zasshi*. Feb 1994;68(2):171-176.
174. Quilty S, Kwok G, Hajkowicz K, Currie B. High incidence of methicillin-resistant *Staphylococcus aureus* sepsis and death in patients with febrile neutropenia at Royal Darwin Hospital. *Intern Med J*. Aug 2009;39(8):557-559.
175. Hakim H, Mylotte JM, Faden H. Morbidity and mortality of Staphylococcal bacteremia in children. *American journal of infection control*. Mar 2007;35(2):102-105.
176. Nickerson EK, Wuthiekanun V, Day NP, Chaowagul W, Peacock SJ. Methicillin-resistant *Staphylococcus aureus* in rural Asia. *The Lancet. Infectious diseases*. Feb 2006;6(2):70-71.
177. Kim SH, Park WB, Lee KD, et al. Outcome of *Staphylococcus aureus* bacteremia in patients with eradicable foci versus noneradicable foci. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Sep 15 2003;37(6):794-799.
178. Melzer M, Eykyn SJ, Gransden WR, Chinn S. Is methicillin-resistant *Staphylococcus aureus* more virulent than methicillin-susceptible *S. aureus*? A comparative cohort study of British patients with nosocomial infection and bacteremia. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Dec 01 2003;37(11):1453-1460.
179. Khatib R, Johnson LB, Fakih MG, et al. Persistence in *Staphylococcus aureus* bacteremia: incidence, characteristics of patients and outcome. *Scandinavian journal of infectious diseases*. 2006;38(1):7-14.
180. Lodise TP, McKinnon PS. Clinical and economic impact of methicillin resistance in patients with *Staphylococcus aureus* bacteremia. *Diagn Microbiol Infect Dis*. Jun 2005;52(2):113-122.
181. Nickerson EK, Hongsuwan M, Limmathurotsakul D, et al. *Staphylococcus aureus* bacteraemia in a tropical setting: patient outcome and impact of antibiotic resistance. *PloS one*. 2009;4(1):e4308.
182. Harbarth S, Rutschmann O, Sudre P, Pittet D. Impact of methicillin resistance on the outcome of patients with bacteremia caused by *Staphylococcus aureus*. *Arch Intern Med*. Jan 26 1998;158(2):182-189.
183. Cunney RJ, McNamara EB, alAnsari N, Smyth EG. Community and hospital acquired *Staphylococcus aureus* septicaemia: 115 cases from a Dublin teaching hospital. *The Journal of infection*. Jul 1996;33(1):11-13.
184. Das I, O'Connell N, Lambert P. Epidemiology, clinical and laboratory characteristics of *Staphylococcus aureus* bacteraemia in a university hospital in UK. *The Journal of hospital infection*. Feb 2007;65(2):117-123.
185. Austin TW, Austin MA, Coleman B. Methicillin-resistant/methicillin-sensitive *Staphylococcus aureus* bacteremia. *Saudi medical journal*. Mar 2003;24(3):256-260.
186. Conterno LO, Wey SB, Castelo A. Risk factors for mortality in *Staphylococcus aureus* bacteremia. *Infection control and hospital epidemiology*. Jan 1998;19(1):32-37.
187. Hill EE, Peetermans WE, Vanderschueren S, Claus P, Herregods MC, Herijgers P. Methicillin-resistant versus methicillin-sensitive *Staphylococcus aureus* infective endocarditis. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology*. Jun 2008;27(6):445-450.
188. Ganga R, Riederer K, Sharma M, et al. Role of SCCmec type in outcome of *Staphylococcus aureus* bacteremia in a single medical center. *J Clin Microbiol*. Mar 2009;47(3):590-595.

189. Burke RE, Halpern MS, Baron EJ, Gutierrez K. Pediatric and neonatal *Staphylococcus aureus* bacteremia: epidemiology, risk factors, and outcome. *Infection control and hospital epidemiology*. Jul 2009;30(7):636-644.
190. de Oliveira Conterno L, Wey SB, Castelo A. *Staphylococcus aureus* bacteremia: comparison of two periods and a predictive model of mortality. *The Brazilian journal of infectious diseases : an official publication of the Brazilian Society of Infectious Diseases*. Dec 2002;6(6):288-297.
191. Lesens O, Methlin C, Hansmann Y, et al. Role of comorbidity in mortality related to *Staphylococcus aureus* bacteremia: a prospective study using the Charlson weighted index of comorbidity. *Infection control and hospital epidemiology*. Dec 2003;24(12):890-896.
192. O'Kane GM, Gottlieb T, Bradbury R. Staphylococcal bacteraemia: the hospital or the home? A review of *Staphylococcus aureus* bacteraemia at Concord Hospital in 1993. *Aust N Z J Med*. Feb 1998;28(1):23-27.
193. de Kraker ME, Wolkewitz M, Davey PG, et al. Clinical impact of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay related to methicillin-resistant *Staphylococcus aureus* bloodstream infections. *Antimicrobial agents and chemotherapy*. Apr 2011;55(4):1598-1605.
194. Salgado CD, Dash S, Cantey JR, Marculescu CE. Higher risk of failure of methicillin-resistant *Staphylococcus aureus* prosthetic joint infections. *Clin Orthop Relat Res*. Aug 2007;461:48-53.
195. Al-Nammari SS, Bobak P, Venkatesh R. Methicillin resistant *Staphylococcus aureus* versus methicillin sensitive *Staphylococcus aureus* adult haematogenous septic arthritis. *Arch Orthop Trauma Surg*. Sep 2007;127(7):537-542.
196. Rello J, Molano D, Villabon M, et al. Differences in hospital- and ventilator-associated pneumonia due to *Staphylococcus aureus* (methicillin-susceptible and methicillin-resistant) between Europe and Latin America: a comparison of the EUVAP and LATINVAP study cohorts. *Med Intensiva*. May 2013;37(4):241-247.
197. Spindel SJ, Strausbaugh LJ, Jacobson C. Infections caused by *Staphylococcus aureus* in a Veterans' Affairs nursing home care unit: a 5-year experience. *Infection control and hospital epidemiology*. Apr 1995;16(4):217-223.
198. Davis SL, Perri MB, Donabedian SM, et al. Epidemiology and outcomes of community-associated methicillin-resistant *Staphylococcus aureus* infection. *J Clin Microbiol*. Jun 2007;45(6):1705-1711.
199. Graffunder EM, Venezia RA. Risk factors associated with nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) infection including previous use of antimicrobials. *The Journal of antimicrobial chemotherapy*. Jun 2002;49(6):999-1005.
200. Priest DH, Peacock JE, Jr. Hematogenous vertebral osteomyelitis due to *Staphylococcus aureus* in the adult: clinical features and therapeutic outcomes. *South Med J*. Sep 2005;98(9):854-862.
201. Hershov RC, Khayr WF, Smith NL. A comparison of clinical virulence of nosocomially acquired methicillin-resistant and methicillin-sensitive *Staphylococcus aureus* infections in a university hospital. *Infection control and hospital epidemiology*. Oct 1992;13(10):587-593.
202. Hulten KG, Kaplan SL, Lamberth LB, et al. Hospital-acquired *Staphylococcus aureus* infections at Texas Children's Hospital, 2001-2007. *Infection control and hospital epidemiology*. Feb 2010;31(2):183-190.
203. Joo EJ, Chung DR, Ha YE, et al. Clinical predictors of community-genotype ST72-methicillin-resistant *Staphylococcus aureus*-SCCmec type IV in patients with community-onset *S. aureus* infection. *The Journal of antimicrobial chemotherapy*. Jul 2012;67(7):1755-1759.

204. Capitano B, Leshem OA, Nightingale CH, Nicolau DP. Cost effect of managing methicillin-resistant *Staphylococcus aureus* in a long-term care facility. *J Am Geriatr Soc*. Jan 2003;51(1):10-16.
205. Clancy MJ, Graepler A, Breese PE, Price CS, Burman WJ. Widespread emergence of methicillin resistance in community-acquired *Staphylococcus aureus* infections in Denver. *South Med J*. Nov 2005;98(11):1069-1075.
206. Rello J, Torres A, Ricart M, et al. Ventilator-associated pneumonia by *Staphylococcus aureus*. Comparison of methicillin-resistant and methicillin-sensitive episodes. *Am J Respir Crit Care Med*. Dec 1994;150(6 Pt 1):1545-1549.
207. Gonzalez C, Rubio M, Romero-Vivas J, Gonzalez M, Picazo JJ. Bacteremic pneumonia due to *Staphylococcus aureus*: A comparison of disease caused by methicillin-resistant and methicillin-susceptible organisms. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Nov 1999;29(5):1171-1177.
208. Pujol M, Pena C, Pallares R, et al. Nosocomial *Staphylococcus aureus* bacteremia among nasal carriers of methicillin-resistant and methicillin-susceptible strains. *Am J Med*. May 1996;100(5):509-516.
209. McMaster J, Booth MG, Smith A, Hamilton K. Methicillin-resistant *Staphylococcus aureus* in the intensive care unit: its effect on outcome and risk factors for acquisition. *The Journal of hospital infection*. Aug 2015;90(4):327-332.
210. Yasmin M, El Hage H, Obeid R, El Haddad H, Zaarour M, Khalil A. Epidemiology of bloodstream infections caused by methicillin-resistant *Staphylococcus aureus* at a tertiary care hospital in New York. *American journal of infection control*. 2016;44(1):41-46.
211. De la Calle C, Morata L, Cobos-Trigueros N, et al. *Staphylococcus aureus* bacteremic pneumonia. *European Journal of Clinical Microbiology and Infectious Diseases*. 2016;35(3):497-502.
212. De Rosa FG, Corcione S, Motta I, et al. Risk factors for mortality in patients with *Staphylococcus aureus* bloodstream infection. *Journal of Chemotherapy*. 2016;28(3):187-190.
213. Deodhar D, Varghese G, Balaji V, et al. Prevalence of toxin genes among the clinical isolates of *Staphylococcus aureus* and its clinical impact. *Journal of Global Infectious Diseases*. 2015;7(3):97-102.
214. Dolapo O, Dhanireddy R, Talati AJ. Trends of *Staphylococcus aureus* bloodstream infections in a neonatal intensive care unit from 2000-2009. *BMC pediatrics*. May 09 2014;14:121.
215. Fortuin-de Smidt MC, Singh-Moodley A, Badat R, et al. *Staphylococcus aureus* bacteraemia in Gauteng academic hospitals, South Africa. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases*. Jan 2015;30:41-48.
216. Kim DH, Tate J, Dresen WF, et al. Cardiac implanted electronic device-related infective endocarditis: clinical features, management, and outcomes of 80 consecutive patients. *Pacing and clinical electrophysiology : PACE*. Aug 2014;37(8):978-985.
217. Kobayashi D, Yokota K, Takahashi O, Arioka H, Fukui T. A predictive rule for mortality of inpatients with *Staphylococcus aureus* bacteraemia: A classification and regression tree analysis. *European journal of internal medicine*. Dec 2014;25(10):914-918.
218. Lee JY, Chong YP, Kim T, et al. Bone and joint infection as a predictor of community-acquired methicillin-resistant *Staphylococcus aureus* bacteraemia: a comparative cohort study. *The Journal of antimicrobial chemotherapy*. Jul 2014;69(7):1966-1971.
219. Manandhar S, Pai G, Gidwani H, et al. Does *staphylococcus aureus* bacteriuria predict clinical outcomes in patients with bacteremia?: Analysis of 274 patients with

- staphylococcus aureus blood stream infection. *Infectious Diseases in Clinical Practice*. 2016;24(3):151-154.
220. McMullan BJ, Bowen A, Blyth CC, et al. Epidemiology and mortality of staphylococcus aureus Bacteremia in Australian and New Zealand children. *JAMA pediatrics*. 2016;170(10):979-986.
221. Nagao M, Yamamoto M, Matsumura Y, et al. Complete adherence to evidence-based quality-of-care indicators for Staphylococcus aureus bacteremia resulted in better prognosis. *Infection*. 2016:1-9.
222. Naidoo R, Nuttall J, Whitelaw A, Eley B. Epidemiology of Staphylococcus aureus bacteraemia at a tertiary children's hospital in Cape Town, South Africa. *PloS one*. 2013;8(10):e78396.
223. Ong CW, Roberts JL, Collignon PJ. Long-term survival outcome following staphylococcus aureus bacteraemia. *Healthcare Infection*. 2013;18(3):102-109.
224. Park DA, Lee SM, Peck KR, Joo EJ, Oh EG. Impact of methicillin-resistance on mortality in children and neonates with staphylococcus aureus bacteremia: A meta-analysis. *Infection and Chemotherapy*. 2013;45(2):202-210.
225. Simsek Yavuz S, Sensoy A, Ceken S, Deniz D, Yekeler I. Methicillin-resistant Staphylococcus aureus infection: an independent risk factor for mortality in patients with poststernotomy mediastinitis. *Medical principles and practice : international journal of the Kuwait University, Health Science Centre*. 2014;23(6):517-523.
226. Thaden JT, Ericson JE, Cross H, et al. Survival benefit of empirical therapy for staphylococcus aureus bloodstream infections in infants. *Pediatric Infectious Disease Journal*. 2015;34(11):1175-1179.
227. Theodorou P, Lefering R, Perbix W, et al. Staphylococcus aureus bacteremia after thermal injury: the clinical impact of methicillin resistance. *Burns : journal of the International Society for Burn Injuries*. May 2013;39(3):404-412.
228. Wang JT, Hsu LY, Lauderdale TL, Fan WC, Wang FD. Comparison of Outcomes among Adult Patients with Nosocomial Bacteremia Caused by Methicillin-Susceptible and Methicillin-Resistant Staphylococcus aureus: A Retrospective Cohort Study. *PloS one*. 2015;10(12).
229. Yaw LK, Robinson JO, Ho KM. A comparison of long-term outcomes after methicillin-resistant and methicillin-sensitive Staphylococcus aureus bacteraemia: an observational cohort study. *The Lancet Infectious Diseases*. 2014.
230. Yilmaz M, Elaldi N, Balkan, et al. Mortality predictors of Staphylococcus aureus bacteremia: A prospective multicenter study. *Annals of Clinical Microbiology and Antimicrobials*. 2016;15(1).
231. Shoji H, Urakawa T, Watanabe K, et al. Clinical features, outcomes, and survival factor in patients with vertebral osteomyelitis infected by methicillin-resistant staphylococci. *Journal of Orthopaedic Science*. 2016;21(3):282-286.
232. Alizadeh N, Oskuee ABE, Golchai J, et al. Methicillin-resistant Staphylococcus aureus (MRSA) an important microorganism: Determination of its prevalence and evaluation of its associated factors in hospitalized dermatologic patients. *Iranian Journal of Dermatology*. 2014;17(68):54-58.
233. Balm MN, Lover AA, Salmon S, Tambyah PA, Fisher DA. Progression from new methicillin-resistant Staphylococcus aureus colonisation to infection: an observational study in a hospital cohort. *BMC infectious diseases*. Oct 22 2013;13:491.
234. Nelson RE, Stevens VW, Jones M, Samore MH, Rubin MA. Health care-associated methicillin-resistant Staphylococcus aureus infections increases the risk of postdischarge mortality. *American journal of infection control*. Jan 2015;43(1):38-43.

235. Tran K, Bell C, Stall N, et al. The Effect of Hospital Isolation Precautions on Patient Outcomes and Cost of Care: A Multi-Site, Retrospective, Propensity Score-Matched Cohort Study. *Journal of General Internal Medicine*. 2016;1-7.
236. Ericson JE, Popoola VO, Smith PB, et al. Burden of Invasive Staphylococcus aureus Infections in Hospitalized Infants. *JAMA pediatrics*. Dec 2015;169(12):1105-1111.
237. Gimenes M, Salci TP, Tognim MCB, Siqueira VLD, Caparroz-Assef SM. Treating Staphylococcus aureus infections in an intensive care unit at a University Hospital in Brazil. *International Journal of Clinical Pharmacy*. 2016;38(2):228-232.
238. Kim ES, Kim HB, Kim G, et al. Clinical and epidemiological factors associated with methicillin resistance in community-onset invasive Staphylococcus aureus infections: prospective multicenter cross-sectional study in Korea. *PloS one*. 2014;9(12):e114127.
239. Altinbas A, Shorbagi A, Ascioğlu S, Zarakolu P, Cetinkaya-Sardan Y. Risk factors for intensive care unit acquired nasal colonization of MRSA and its impact on MRSA infection. *Journal of clinical laboratory analysis*. Sep 2013;27(5):412-417.
240. Chan TC, Cheng VC, Hung IF, Chan FH, Ng WC, Yuen KY. The association between methicillin resistant staphylococcus aureus colonization and mortality in Chinese nursing home older adults: a 2-year prospective cohort. *Journal of the American Medical Directors Association*. Sep 01 2015;16(9):796-797.
241. Chen CC, Pass SE. Risk factors for and impact of methicillin-resistant Staphylococcus aureus nasal colonization in patients in a medical intensive care unit. *American journal of infection control*. Nov 2013;41(11):1100-1101.
242. Moore C, Davis NF, Burke JP, et al. Colonisation with methicillin-resistant Staphylococcus aureus prior to renal transplantation is associated with long-term renal allograft failure. *Transplant international : official journal of the European Society for Organ Transplantation*. Sep 2014;27(9):926-930.
243. Minejima E, Lou M, Nieberg P, Wong-Beringer A. Patients presenting to the hospital with MRSA pneumonia: differentiating characteristics and outcomes with empiric treatment. *BMC infectious diseases*. May 10 2014;14:252.
244. Hill DM, Schroepfel TJ, Magnotti LJ, et al. Methicillin-resistant Staphylococcus aureus in early ventilator-associated pneumonia: cause for concern? *Surgical infections*. Dec 2013;14(6):520-524.
245. Tosh PK, Bulens SN, Nadle J, et al. Characterization of hospitalized community-onset staphylococcus aureus lower respiratory tract infections among generally healthy persons 50 years of age or younger. *Infectious Diseases in Clinical Practice*. 2013;21(6):359-365.
246. Jung WJ, Kang YA, Park MS, et al. Prediction of methicillin-resistant Staphylococcus aureus in patients with non-nosocomial pneumonia. *BMC infectious diseases*. Aug 09 2013;13:370.
247. Self WH, Wunderink RG, Williams DJ, et al. Staphylococcus aureus Community-acquired Pneumonia: Prevalence, Clinical Characteristics, and Outcomes. *Clinical Infectious Diseases*. 2016;63(3):300-309.
248. Lin WT, Wu CD, Cheng SC, et al. High Prevalence of Methicillin-Resistant Staphylococcus aureus among Patients with Septic Arthritis Caused by Staphylococcus aureus. *PloS one*. 2015;10(5):e0127150.
249. Mínguez S, Molinos S, Mateo L, et al. Septic arthritis due to methylcyllin-resistant Staphylococcus aureus in adults. *Reumatologia Clinica*. 2015;11(6):381-386.
250. de Kraker ME, Davey PG, Grundmann H, group Bs. Mortality and hospital stay associated with resistant Staphylococcus aureus and Escherichia coli bacteremia: estimating the burden of antibiotic resistance in Europe. *PLoS Med*. Oct 2011;8(10):e1001104.

251. Bender R, Blettner M. Calculating the "number needed to be exposed" with adjustment for confounding variables in epidemiological studies. *J Clin Epidemiol*. May 2002;55(5):525-530.
252. Liu Q, Li X, Li W, et al. Influence of carbapenem resistance on mortality of patients with *Pseudomonas aeruginosa* infection: a meta-analysis. *Scientific reports*. Jun 25 2015;5:11715.
253. Dantas RC, Ferreira ML, Gontijo-Filho PP, Ribas RM. *Pseudomonas aeruginosa* bacteraemia: independent risk factors for mortality and impact of resistance on outcome. *Journal of medical microbiology*. Dec 2014;63(Pt 12):1679-1687.
254. Hattemer A, Hauser A, Diaz M, et al. Bacterial and clinical characteristics of health care- and community-acquired bloodstream infections due to *Pseudomonas aeruginosa*. *Antimicrobial agents and chemotherapy*. Aug 2013;57(8):3969-3975.
255. Joo EJ, Kang CI, Ha YE, et al. Risk factors for mortality in patients with *Pseudomonas aeruginosa* bacteremia: clinical impact of antimicrobial resistance on outcome. *Microbial drug resistance (Larchmont, N.Y.)*. Jun 2011;17(2):305-312.
256. Kang CI, Kim SH, Park WB, et al. Risk factors for antimicrobial resistance and influence of resistance on mortality in patients with bloodstream infection caused by *Pseudomonas aeruginosa*. *Microbial drug resistance (Larchmont, N.Y.)*. Spring 2005;11(1):68-74.
257. Kim YJ, Jun YH, Kim YR, et al. Risk factors for mortality in patients with *Pseudomonas aeruginosa* bacteremia; retrospective study of impact of combination antimicrobial therapy. *BMC infectious diseases*. Mar 24 2014;14:161.
258. Pena C, Suarez C, Gozalo M, et al. Prospective multicenter study of the impact of carbapenem resistance on mortality in *Pseudomonas aeruginosa* bloodstream infections. *Antimicrobial agents and chemotherapy*. Mar 2012;56(3):1265-1272.
259. Suarez C, Pena C, Gavalda L, et al. Influence of carbapenem resistance on mortality and the dynamics of mortality in *Pseudomonas aeruginosa* bloodstream infection. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases*. Sep 2010;14 Suppl 3:e73-78.
260. Tuon FF, Gortz LW, Rocha JL. Risk factors for pan-resistant *Pseudomonas aeruginosa* bacteremia and the adequacy of antibiotic therapy. *The Brazilian journal of infectious diseases : an official publication of the Brazilian Society of Infectious Diseases*. Jul-Aug 2012;16(4):351-356.
261. Luyt CE, Aubry A, Lu Q, et al. Imipenem, meropenem or doripenem to treat patients with *pseudomonas aeruginosa* ventilator-associated pneumonia. *American Journal of Respiratory and Critical Care Medicine*. 2014;189.
262. Eagye KJ, Kuti JL, Nicolau DP. Risk factors and outcomes associated with isolation of meropenem high-level-resistant *Pseudomonas aeruginosa*. *Infection control and hospital epidemiology*. Aug 2009;30(8):746-752.
263. Judd WR, Ratliff PD, Hickson RP, Stephens DM, Kennedy CA. Clinical and economic impact of meropenem resistance in *Pseudomonas aeruginosa*-infected patients. *American journal of infection control*. 2016;44(11):1275-1279.
264. Lautenbach E, Weiner MG, Nachamkin I, Bilker WB, Sheridan A, Fishman NO. Imipenem resistance among *pseudomonas aeruginosa* isolates: risk factors for infection and impact of resistance on clinical and economic outcomes. *Infection control and hospital epidemiology*. Sep 2006;27(9):893-900.
265. Lautenbach E, Synnestvedt M, Weiner MG, et al. Imipenem resistance in *Pseudomonas aeruginosa*: emergence, epidemiology, and impact on clinical and economic outcomes. *Infection control and hospital epidemiology*. Jan 2010;31(1):47-53.



266. Lin KY, Lauderdale TL, Wang JT, Chang SC. Carbapenem-resistant *Pseudomonas aeruginosa* in Taiwan: Prevalence, risk factors, and impact on outcome of infections. *Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi*. Feb 2016;49(1):52-59.
267. Meradji S, Barguigua A, Zerouali K, et al. Epidemiology of carbapenem non-susceptible *Pseudomonas aeruginosa* isolates in Eastern Algeria. *Antimicrobial Resistance and Infection Control*. 2015;4(1).
268. The cost of antibiotic resistance: effect of resistance among *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* on length of hospital stay. *Infection control and hospital epidemiology*. Feb 2002;23(2):106-108.
269. Matthaiou DK, Michalopoulos A, Rafailidis PI, et al. Risk factors associated with the isolation of colistin-resistant Gram-negative bacteria: A matched case-control study. *Critical Care Medicine*. 2008;36(3):807-811.
270. Yilmaz GR, Dizbay M, Guven T, et al. Risk factors for infection with colistin-resistant gram-negative microorganisms: A multicenter study. *Annals of Saudi Medicine*. 2016;36(3):216-222.
271. Caselli D, Cesaro S, Ziino O, et al. Multidrug resistant *Pseudomonas aeruginosa* infection in children undergoing chemotherapy and hematopoietic stem cell transplantation. *Haematologica*. Sep 2010;95(9):1612-1615.
272. Johnson LE, D'Agata EM, Paterson DL, et al. *Pseudomonas aeruginosa* bacteremia over a 10-year period: multidrug resistance and outcomes in transplant recipients. *Transplant infectious disease : an official journal of the Transplantation Society*. Jun 2009;11(3):227-234.
273. Morata L, Cobos-Trigueros N, Martinez JA, et al. Influence of multidrug resistance and appropriate empirical therapy on the 30-day mortality rate of *Pseudomonas aeruginosa* bacteremia. *Antimicrobial agents and chemotherapy*. Sep 2012;56(9):4833-4837.
274. Tam VH, Rogers CA, Chang KT, Weston JS, Caeiro JP, Garey KW. Impact of multidrug-resistant *Pseudomonas aeruginosa* bacteremia on patient outcomes. *Antimicrobial agents and chemotherapy*. Sep 2010;54(9):3717-3722.
275. Theodorou P, Thamm OC, Perbix W, Phan VT. *Pseudomonas aeruginosa* bacteremia after burn injury: the impact of multiple-drug resistance. *Journal of burn care & research : official publication of the American Burn Association*. Nov-Dec 2013;34(6):649-658.
276. Trecarichi EM, Tumbarello M, Caira M, et al. Multidrug resistant *Pseudomonas aeruginosa* bloodstream infection in adult patients with hematologic malignancies. *Haematologica*. Jan 2011;96(1):e1-3; author reply e4.
277. Tumbarello M, Repetto E, Trecarichi EM, et al. Multidrug-resistant *Pseudomonas aeruginosa* bloodstream infections: risk factors and mortality. *Epidemiology and infection*. Nov 2011;139(11):1740-1749.
278. Cillóniz C, Gabarrús A, Ferrer M, et al. Community-Acquired Pneumonia Due to Multidrug- and Non-Multidrug-Resistant *Pseudomonas aeruginosa*. *Chest*. 2016;150(2):415-425.
279. Montero M, Dominguez M, Orozco-Levi M, Salvado M, Knobel H. Mortality of COPD patients infected with multi-resistant *Pseudomonas aeruginosa*: a case and control study. *Infection*. Feb 2009;37(1):16-19.
280. Micek ST, Wunderink RG, Kollef MH, et al. An international multicenter retrospective study of *Pseudomonas aeruginosa* nosocomial pneumonia: impact of multidrug resistance. *Critical care (London, England)*. May 06 2015;19:219.
281. Pena C, Gomez-Zorrilla S, Oriol I, et al. Impact of multidrug resistance on *Pseudomonas aeruginosa* ventilator-associated pneumonia outcome: predictors of early and crude

- mortality. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology*. Mar 2013;32(3):413-420.
282. Tumbarello M, De Pascale G, Treccarichi EM, et al. Clinical outcomes of *Pseudomonas aeruginosa* pneumonia in intensive care unit patients. *Intensive care medicine*. Apr 2013;39(4):682-692.
283. Yang K, Zhuo H, Guglielmo BJ, Wiener-Kronish J. Multidrug-resistant *Pseudomonas aeruginosa* ventilator-associated pneumonia: the role of endotracheal aspirate surveillance cultures. *The Annals of pharmacotherapy*. Jan 2009;43(1):28-35.
284. Yayan J, Ghebremedhin B, Rasche K. Antibiotic resistance of *pseudomonas aeruginosa* in pneumonia at a single university hospital center in Germany over a 10-Year Period. *PloS one*. 2015;10(10).
285. Aloush V, Navon-Venezia S, Seigman-Igra Y, Cabili S, Carmeli Y. Multidrug-resistant *Pseudomonas aeruginosa*: risk factors and clinical impact. *Antimicrobial agents and chemotherapy*. Jan 2006;50(1):43-48.
286. Paramythiotou E, Lucet JC, Timsit JF, et al. Acquisition of multidrug-resistant *Pseudomonas aeruginosa* in patients in intensive care units: role of antibiotics with antipseudomonal activity. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Mar 1 2004;38(5):670-677.
287. Cao B, Wang H, Sun H, Zhu Y, Chen M. Risk factors and clinical outcomes of nosocomial multi-drug resistant *Pseudomonas aeruginosa* infections. *The Journal of hospital infection*. Jun 2004;57(2):112-118.
288. de Matos ECO, De Matos HJ, Conceição ML, Rodrigues YC, Carneiro ICRS, Lima KVB. Clinical and microbiological features of infections caused by *pseudomonas aeruginosa* in patients hospitalized in intensive care units. *Revista da Sociedade Brasileira de Medicina Tropical*. 2016;49(3):305-311.
289. Morales E, Cots F, Sala M, et al. Hospital costs of nosocomial multi-drug resistant *Pseudomonas aeruginosa* acquisition. *BMC health services research*. May 23 2012;12:122.
290. Nathwani D, Raman G, Sulham K, Gavaghan M, Menon V. Clinical and economic consequences of hospital-acquired resistant and multidrug-resistant *Pseudomonas aeruginosa* infections: A systematic review and meta-analysis. *Antimicrobial Resistance and Infection Control*. 2014;3(1).
291. Ortega B, Groeneveld AB, Schultz C. Endemic multidrug-resistant *Pseudomonas aeruginosa* in critically ill patients. *Infection control and hospital epidemiology*. Oct 2004;25(10):825-831.
292. Peng Y, Bi J, Shi J, et al. Multidrug-resistant *Pseudomonas aeruginosa* infections pose growing threat to health care-associated infection control in the hospitals of Southern China: A case-control surveillance study. *American journal of infection control*. 2014;42(12):1308-1311.
293. Su H, Ye Q, Wan Q, Zhou J. Predictors of Mortality in Abdominal Organ Transplant Recipients with *Pseudomonas aeruginosa* Infections. *Annals of transplantation*. Feb 09 2016;21:86-93.
294. Tleyjeh IM, Tlaygeh HM, Hejal R, Montori VM, Baddour LM. The impact of penicillin resistance on short-term mortality in hospitalized adults with pneumococcal pneumonia: a systematic review and meta-analysis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Mar 15 2006;42(6):788-797.
295. Yu VL, Chiou CC, Feldman C, et al. An international prospective study of pneumococcal bacteremia: correlation with in vitro resistance, antibiotics administered, and clinical outcome. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Jul 15 2003;37(2):230-237.

296. Watanabe H, Sato S, Kawakami K, et al. A comparative clinical study of pneumonia by penicillin-resistant and -sensitive *Streptococcus pneumoniae* in a community hospital. *Respirology*. Mar 2000;5(1):59-64.
297. Gouveia EL, Reis JN, Flannery B, et al. Clinical outcome of pneumococcal meningitis during the emergence of penicillin-resistant *Streptococcus pneumoniae*: an observational study. *BMC infectious diseases*. 2011;11:323.
298. Reechaipichitkul W, Assawasanti K, Chaimanee P. Risk factors and clinical outcomes of penicillin resistant *S. pneumoniae* community-acquired pneumonia in Khon Kaen, Thailand. *The Southeast Asian journal of tropical medicine and public health*. Mar 2006;37(2):320-326.
299. Sun HK, Nicolau DP, Kuti JL. Resource utilization of adults admitted to a large urban hospital with community-acquired pneumonia caused by *Streptococcus pneumoniae*. *Chest*. Sep 2006;130(3):807-814.
300. Song JH, Jung SI, Ki HK, et al. Clinical outcomes of pneumococcal pneumonia caused by antibiotic-resistant strains in Asian countries: a study by the Asian Network for Surveillance of Resistant Pathogens. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Jun 1 2004;38(11):1570-1578.
301. Einarsson S, Kristjansson M, Kristinsson KG, Kjartansson G, Jonsson S. Pneumonia caused by penicillin-non-susceptible and penicillin-susceptible pneumococci in adults: a case-control study. *Scandinavian journal of infectious diseases*. 1998;30(3):253-256.
302. Sangthawan P, Chantaratchada S, Chanthadisai N, Wattanatham A. Prevalence and clinical significance of community-acquired penicillin-resistant pneumococcal pneumonia in Thailand. *Respirology*. Jun 2003;8(2):208-212.
303. Falco V, Almirante B, Jordano Q, et al. Influence of penicillin resistance on outcome in adult patients with invasive pneumococcal pneumonia: is penicillin useful against intermediately resistant strains? *The Journal of antimicrobial chemotherapy*. Aug 2004;54(2):481-488.
304. Pallares R, Linares J, Vadillo M, et al. Resistance to penicillin and cephalosporin and mortality from severe pneumococcal pneumonia in Barcelona, Spain. *N Engl J Med*. Aug 24 1995;333(8):474-480.
305. Ewig S, Ruiz M, Torres A, et al. Pneumonia acquired in the community through drug-resistant *Streptococcus pneumoniae*. *Am J Respir Crit Care Med*. Jun 1999;159(6):1835-1842.
306. Aspa J, Rajas O, Rodriguez de Castro F, et al. Drug-resistant pneumococcal pneumonia: clinical relevance and related factors. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Mar 15 2004;38(6):787-798.
307. Feikin DR, Schuchat A, Kolczak M, et al. Mortality from invasive pneumococcal pneumonia in the era of antibiotic resistance, 1995-1997. *Am J Public Health*. Feb 2000;90(2):223-229.
308. Yigla M, Finkelstein R, Hashman N, Green P, Cohn L, Merzbach D. Epidemiology and clinical spectrum of pneumococcal infections: an Israeli viewpoint. *The Journal of hospital infection*. Jan 1995;29(1):57-64.
309. Pallares R, Capdevila O, Linares J, et al. The effect of cephalosporin resistance on mortality in adult patients with nonmeningeal systemic pneumococcal infections. *Am J Med*. Aug 01 2002;113(2):120-126.
310. Jehl FB, JP.; Poirer, R.; Leophonte, P.; Sirot, J.; Chardon H. Enquête nationale sur les pneumonies communautaires à pneumocoque chez des malades adultes hospitalisés. *Médecine et maladies infectieuses*. 2002;+

32(6):267-283.

311. Weinstein MP, Klugman KP, Jones RN. Rationale for revised penicillin susceptibility breakpoints versus *Streptococcus pneumoniae*: coping with antimicrobial susceptibility in an era of resistance. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Jun 1 2009;48(11):1596-1600.
312. Carmeli Y, Eliopoulos G, Mozaffari E, Samore M. Health and economic outcomes of vancomycin-resistant enterococci. *Arch Intern Med*. Oct 28 2002;162(19):2223-2228.
313. DiazGranados CA, Zimmer SM, Klein M, Jernigan JA. Comparison of mortality associated with vancomycin-resistant and vancomycin-susceptible enterococcal bloodstream infections: a meta-analysis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Aug 1 2005;41(3):327-333.
314. Salgado CD, Farr BM. Outcomes associated with vancomycin-resistant enterococci: a meta-analysis. *Infection control and hospital epidemiology*. Sep 2003;24(9):690-698.
315. da Silva NS, Muniz VD, Estofolete CF, Furtado GH, Rubio FG. Identification of temporal clusters and risk factors of bacteremia by nosocomial vancomycin-resistant enterococci. *American journal of infection control*. Apr 2014;42(4):389-392.
316. Yoo J-H, Lee, D-G., Choi, SM., Choi, J-H., Shin, W-S., Kim, M., Yong, D., Lee, K., Min, W-S., Kim, C-C. Vancomycin-resistant Enterococcal Bacteremia in a Hematology Unit: Molecular Epidemiology and Analysis of Clinical Course. *Journal of Korean medical science*. 2005;20:169-176.
317. Lodise TP, McKinnon PS, Tam VH, Rybak MJ. Clinical outcomes for patients with bacteremia caused by vancomycin-resistant enterococcus in a level 1 trauma center. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Apr 1 2002;34(7):922-929.
318. Peset V, Tallon P, Sola C, et al. Epidemiological, microbiological, clinical, and prognostic factors of bacteremia caused by high-level vancomycin-resistant *Enterococcus* species. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology*. Oct 2000;19(10):742-749.
319. Garbutt JM, Ventrapragada M, Littenberg B, Mundy LM. Association between resistance to vancomycin and death in cases of *Enterococcus faecium* bacteremia. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Mar 2000;30(3):466-472.
320. Bhavnani S, Drake, JA., Forrest, A., Deinhart, JA., Jones, RN. Biedenbach, DJ., Ballow, CH. Nationwide, multicenter, case-control study comparing risk factors, treatment, and outcome for vancomycin-resistant and -susceptible enterococcal bacteremia. *Diagn Microbiol Infect Dis*. 2000;36:145-158.
321. Lucas GM, Lechtzin N, Puryear DW, Yau LL, Flexner CW, Moore RD. Vancomycin-resistant and vancomycin-susceptible enterococcal bacteremia: comparison of clinical features and outcomes. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. May 1998;26(5):1127-1133.
322. Stosor V, Peterson LR, Postelnick M, Noskin GA. *Enterococcus faecium* bacteremia: does vancomycin resistance make a difference? *Arch Intern Med*. Mar 9 1998;158(5):522-527.
323. Linden PK, Pasculle AW, Manez R, et al. Differences in outcomes for patients with bacteremia due to vancomycin-resistant *Enterococcus faecium* or vancomycin-susceptible *E. faecium*. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Apr 1996;22(4):663-670.
324. Krcmery V, Bilikova E, Svetlansky I, Kovacicova G. Is vancomycin resistance in enterococci predictive of inferior outcome of enterococcal bacteremia? *Clinical infectious diseases : an*

*official publication of the Infectious Diseases Society of America*. Apr 1 2001;32(7):1110-1112.

325. Vergis EN, Hayden MK, Chow JW, et al. Determinants of vancomycin resistance and mortality rates in enterococcal bacteremia. a prospective multicenter study. *Annals of internal medicine*. Oct 2 2001;135(7):484-492.
326. Shay DK, Maloney SA, Montecalvo M, et al. Epidemiology and mortality risk of vancomycin-resistant enterococcal bloodstream infections. *J Infect Dis*. Oct 1995;172(4):993-1000.
327. Wells CL, Juni BA, Cameron SB, et al. Stool carriage, clinical isolation, and mortality during an outbreak of vancomycin-resistant enterococci in hospitalized medical and/or surgical patients. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Jul 1995;21(1):45-50.
328. Cheah AL, Spelman T, Liew D, et al. Enterococcal bacteraemia: factors influencing mortality, length of stay and costs of hospitalization. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. Apr 2013;19(4):E181-189.
329. DiazGranados CA, Jernigan JA. Impact of vancomycin resistance on mortality among patients with neutropenia and enterococcal bloodstream infection. *J Infect Dis*. Feb 15 2005;191(4):588-595.
330. Peel T, Cheng AC, Spelman T, Huysmans M, Spelman D. Differing risk factors for vancomycin-resistant and vancomycin-sensitive enterococcal bacteraemia. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. Apr 2012;18(4):388-394.
331. Mainous MR, Lipsett PA, O'Brien M. Enterococcal bacteremia in the surgical intensive care unit. Does vancomycin resistance affect mortality? The Johns Hopkins SICU Study Group. *Arch Surg*. Jan 1997;132(1):76-81.
332. Centers for Disease C, Prevention. Nosocomial enterococci resistant to vancomycin-- United States, 1989-1993. *MMWR Morb Mortal Wkly Rep*. Aug 06 1993;42(30):597-599.
333. Lautenbach E, Bilker WB, Brennan PJ. Enterococcal bacteremia: risk factors for vancomycin resistance and predictors of mortality. *Infection control and hospital epidemiology*. May 1999;20(5):318-323.
334. Stroud L, Edwards J, Danzing L, Culver D, Gaynes R. Risk factors for mortality associated with enterococcal bloodstream infections. *Infection control and hospital epidemiology*. Sep 1996;17(9):576-580.
335. Song X, Srinivasan A, Plaut D, Perl TM. Effect of nosocomial vancomycin-resistant enterococcal bacteremia on mortality, length of stay, and costs. *Infection control and hospital epidemiology*. Apr 2003;24(4):251-256.
336. Edmond MB, Ober JF, Dawson JD, Weinbaum DL, Wenzel RP. Vancomycin-resistant enterococcal bacteremia: natural history and attributable mortality. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Dec 1996;23(6):1234-1239.
337. Edmond MB, Ober JF, Weinbaum DL, et al. Vancomycin-resistant *Enterococcus faecium* bacteremia: risk factors for infection. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. May 1995;20(5):1126-1133.
338. Butler AM, Olsen MA, Merz LR, et al. Attributable costs of enterococcal bloodstream infections in a nonsurgical hospital cohort. *Infection control and hospital epidemiology*. Jan 2010;31(1):28-35.

339. Khair HN, VanTassell P, Henderson JP, Warren DK, Marschall J, Program CDCPE. Vancomycin resistance has no influence on outcomes of enterococcal bacteriuria. *The Journal of hospital infection*. Nov 2013;85(3):183-188.
340. Tornieporth NG, Roberts RB, John J, Hafner A, Riley LW. Risk factors associated with vancomycin-resistant *Enterococcus faecium* infection or colonization in 145 matched case patients and control patients. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Oct 1996;23(4):767-772.

## Burden of antimicrobial resistance

### Literature selection grids

Alessandro Cassini and Diamantis Plachouras with contributions from Ana Hoxha, Liselotte Diaz Högberg and Carl Suetens

|  |   |
|--|---|
| <b>Sample size</b>                             | <b>N</b> refers to total number of cases and controls ( <b>no score</b> )   |
| <b>Study type</b>                              | <b>Calculation a priori:</b> ++ if performed (e.g. based on expected prevalence or on literature data) or the study refers to large national surveys; - if not performed  |
| <b>Infection type</b>                          | <b>Study type:</b> ++ matched cohort or case-control studies; + prospective cohort or case-control studies; - retrospective database studies<br><b>HCA:</b> health-care associated; <b>CA:</b> community associated; <b>Mix:</b> health-care and community associated together  |
| <b>Representativeness</b>                      | <b>Geographical:</b> ++ if the study was conducted in an EU/EEA setting; + if the study was conducted in high-income country(ref. World bank); - if the study was not conducted in an EU/EEA or high-income country<br><b>Demographical:</b> ++ if the study population represents all age groups; + if the study population represents selected age-specific groups (e.g. elderly, infants); - if the study population represents a disease-specific population<br><b>Clinical:</b> ++ if the study population represents the overall hospital population; + if the study population partially represents the hospital population; - if the study population represents a disease-specific population<br><b>Exclusion/inclusion criteria:</b> ++ if the same exclusion/inclusion criteria were adopted for both cases and controls; + if some (but not all) exclusion/inclusion criteria were adopted for both cases and controls; - if not performed at all<br><b>Demographics:</b> ++ if performed for age and sex; + if performed only for age or only for sex; - if not performed at all |
| <b>Matching or controlling for confounders</b> | <b>Underlying disease:</b> ++ if performed for two or more criteria (e.g. comorbidity score, McCabe score, severity index, n. comorbidities, allergy, immunosuppression status, prior hospitalisation etc.); + if performed for one criterion; - if not performed<br><b>Infection site:</b> ++ if performed; - if not performed<br><b>Hospital and unit/ward:</b> ++ if same hospital and same unit/ward; + if same hospital but different unit/ward; - if not same hospital and/or not same unit/ward<br><b>Follow-up:</b> ++ if ≥ 28 days; - if < 28 days   |
| <b>Risk difference</b>                         | <b>Statistically significant outcome results:</b> ++ if results and 95%CI are statistically significant; - if results and 95%CI are not statistically significant<br><b>Case fatality and LOS</b> refer to risk difference estimates in cases and controls ( <b>no score</b> )  |

**Scoring table**

|        |   |
|--------|---|
| ++     | Matches completely/is completely fulfilled                                      |
| +      | Matches incompletely but sufficiently/is only partly but sufficiently fulfilled |
| -      | Does not match or matches insufficiently/is insufficiently fulfilled            |
| c.b.e. | Cannot be evaluated   |



etting

tegory and age-specific groups

(e.g. liver transplanted patients, cancer patients, etc..) xclusion/inclusion

criteria were different in cases and controls

for only one criteria; - if not performed at all

|          |   |
|----------|---|
| 3GCREC   | third-generation cephalosporin-resistant <i>E. coli</i>   |
| 3GCRKP   | third-generation cephalosporin-resistant <i>K. pneumoniae</i>   |
| AMR      | antimicrobial resistance  |
| BSI      | bloodstream infection   |
| CAI      | Community-associated infections   |
| CI       | confidence interval   |
| ColRACI  | colistin-resistant <i>Acinetobacter</i> spp.  |
| ColREC   | colistin-resistant <i>E. coli</i>   |
| ColRKP   | colistin-resistant <i>K. pneumoniae</i>   |
| ColRPA   | colistin-resistant <i>P. aeruginosa</i>   |
| CRACI    | carbapenem-resistant <i>Acinetobacter</i> spp.  |
| CREC     | carbapenem-resistant <i>E. coli</i>   |
| CRKP     | carbapenem-resistant <i>K. pneumoniae</i>   |
| CRPA     | carbapenem-resistant <i>P. aeruginosa</i>   |
| CSF      | cerebral spine fluid  |
| DALY     | disability-adjusted life years  |
| EARS-Net | European Antimicrobial Resistance Surveillance Network  |
| EEA      | European Economic Area  |
| EU       | European Union  |
| HAI      | healthcare-associated infection   |
| LOS      | length of stay  |
| MDR      | multidrug-resistant   |
| MDRACI   | multidrug-resistant <i>Acinetobacter</i> spp  |
| MDRPA    | multidrug-resistant <i>P. aeruginosa</i>  |
| MRSA     | meticillin-resistant <i>Staphylococcus aureus</i>   |
| MS       | Member State  |
| OECD     | Organisation for Economic Co-operation and Development  |
| OTH      | other infection site including digestive tract infections, skin and soft tissue infections (SSTI), eye, ear, nose or mouth infections, bone and joint infections, cardiovascular infections, reproductive tract infections and other less frequent infections |
| PMRSP    | penicillin- and macrolide-resistant <i>S. pneumoniae</i>  |
| PPS      | point prevalence survey of healthcare-associated infections and antimicrobial use in acute care hospitals   |
| PRSP     | penicillin-resistant <i>S. pneumoniae</i> ;   |
| RESP     | respiratory infections (including pneumonia, and low respiratory tract infection)   |
| S-BSI    | secondary BSI   |
| SP       | specified pathogens   |
| SPDAR    | specified pathogens with defined antimicrobial resistance   |
| SSI      | surgical site infection   |
| UTI      | urinary tract infection   |
| VRE      | vancomycin-resistant enterococci  |

**CRISP** list for the evaluation of the most relevant studies for building antimicrobial resistance (AMR) outcome trees, healthcare-associated infection (HAI) attributable case fatality and attributable length-of-stay (LOS)

| Study          | Study type         | Infection type       | Sample size         |  | Representativeness   |   |               | Matching or controlling for confounders |               |                    |                |   | Statistically significant outcome results  | Risk difference   |  |  |  |   |   |
|----------------|--------------------|----------------------|---------------------|--|--|---|---------------|---|---------------|--------------------|----------------|---|--|---|--|--|--|---|---|
|                |                    |                      | N (cases/controls)  | calculation a priori   | Geographical   | Demographical   | Clinical      | Exclusion/inclusion criteria            | Demographics  | Underlying disease | Infection site | Hospital and unit/ward  |  | Follow-up   | Case fatality  | LOS  |  |   |   |
| Nr             | First author, year |                      | HCA; CA; Mix; c.b.e |  | □++□□□□□□□□  | □++□+□□□□□□□□   | □++□□□□□□□□□□ | □++□□□□□□□□□□                           | □++□□□□□□□□□□ | □++□□□□□□□□□□      | □++□□□□□□□□□□  | □++□□□□□□□□□□   | □++□□□□□□□□□□  | □++□□□□□□□□□□   | □++□□□□□□□□□□  | □++□□□□□□□□□□  |  |   |   |
| BSI<br>R vs NI | 1                  | Gallagher, 2014      | Score               | ++   | c.b.e  | 111 cases<br>111 controls   | -             | +                                       | ++            | ++                 | ++             | -   | -  | -   | ++   | c.b.e  | ++   | Mort. rate cases=32%<br>Mort. rate controls=13%<br>OR=3.6, 95%CI(1.2 to 10.5)   | mean cases=63<br>controls=20  |
|                |                    |                      | Comments            | Matched Case-control study (matched only by month/year and unit) | no information in the article  |   |               |   |               |                    |                |   | no univariate analyses   | no univariate analyses  | R vs NI  | mortality in hospital                                |  |   |   |
| BSI<br>R vs S  | 2                  | Stewardson, 2016     | Score               | -  | Mix  | 360 cases<br>2100 controls<br>904797 NI   | ++            | ++                                      | ++            | +                  | ++             | -   | -  | -   | -  | c.b.e  | ++   | Mort. rate resistant=16.1%<br>Mort. rate sensitive=10.1%<br>Mort. rate NI=1.7%<br>R vs NI: HR=2.88/2.25/1.80<br>R vs S: HR=1.39/1.43/1.63                   | no specific data, see full-text for modelling values  |
|                |                    |                      | Comments            | Multicentre retrospective cohort study                           | HCA: 59.4% cases, 17.1% controls; community onset: 40.6% cases, 62.9% controls | the study analysed Enterobacteriaceae (E. coli, K. spp. and Proteus spp.), but included because of its methodological value |               |   |               |                    |                | patients with acute-care episodes lasting more than one day   | no univariate analyses matched in model 2  | no univariate analyses  | all BSI or NI  | mortality in hospital                                | all HR   |   | * the study models the excess in LOS and mortality between groups proposing 3 models for each           |
| BSI<br>R vs S  | 1                  | Lee, 2014            | Score               | -  | CA   | 9 cases<br>153 controls   | -             | +                                       | ++            | ++                 | ++             | -   | -  | -   | +  | ++   | -  | a) Mort. rate cases=33.3%<br>Mort. rate controls=24.2%<br>b) Mort. rate cases=33.3%<br>Mort. rate controls=16.3%  | no data   |
|                |                    |                      | Comments            | Retrospective case-control study                                 |  |   |               |   |               |                    |                |   | no univariate analyses   | no univariate analyses  | all BSI  | a)30 day mortality<br>b)bacteremia-related mortality |  |   | a)30 day mortality<br>b)bacteremia-related mortality  |
| BSI<br>R vs S  | 2                  | Panhotra, 2014       | Score               | -  | HCA  | 10 cases<br>16 controls   | -             | +                                       | ++            | ++                 | ++             | -   | -  | -   | +  | c.b.e  | ++   | Mort. rate cases=60%<br>Mort. rate controls=6.2%  | cases=44.2<br>controls=24.1   |
|                |                    |                      | Comments            | Retrospective case-control study                                 |  |   |               |   |               |                    |                |   |  |   | all BSI  | mortality in hospital                                |  |   |   |
| BSI<br>R vs S  | 3                  | Tumbarello, 2006     | Score               | -  | Mix  | 48 cases<br>99 controls   | -             | ++                                      | ++            | ++                 | ++             | +   | ++   | -   | +  | ++   | ++   | a) Mort. rate cases=25%<br>Mort. rate controls=11%<br>b) Mort. rate cases=52%<br>Mort. rate controls=29%<br>OR=2.62; 95%CI(1.28-5.35)                       | mean ± SD cases=34±20<br>controls=31±17   |
|                |                    |                      | Comments            | Retrospective case-control study                                 | HCA: 96% cases, 82% controls   |   |               |   |               |                    |                | not matched but controlled in univariate analyses for gender, age was higher in                         | not matched but controlled in univariate analyses for Charlson index, APACHE II score and main | all BSI   | a)7 days<br>b)21 days  |  |  | a)7 days<br>b)21 days   |   |
| BSI<br>R vs S  | 4                  | Marra, 2006          | Score               | -  | HCA  | 56 cases<br>52 controls   | -             | -                                       | ++            | ++                 | ++             | ++  | ++   | -   | +  | ++   | ++   | Mort. rate cases=32%<br>Mort. rate controls=15%   | no specific data  |
|                |                    |                      | Comments            | Retrospective cohort study                                       |  |   |               |   |               |                    |                | included adults and infants   | not matched but controlled in univariate analyses  | not matched but controlled in univariate analyses for McCabe score and nr. Of comorbidities | all BSI  | 15 days  |  |   |   |
| BSI<br>R vs S  | 5                  | Kang, 2004           | Score               | -  | Mix  | 10 cases<br>20 controls   | -             | +                                       | ++            | ++                 | ++             | ++  | ++   | -   | +  | ++   | c.b.e  | Mort. rate cases=60%<br>Mort. rate controls=30%   |   |
|                |                    |                      | Comments            | Retrospective cohort study                                       | HCA: 93.3% cases, 93.3% controls   |   |               |   |               |                    |                | all patients had liver cholestasis and spontaneous bacterial peritonitis                                | not matched but controlled in univariate analyses  | matched for Child-Pugh score (severity of cholestasis) and APACHE II score                  | all BSI  | 30 days  |  |   | no test for KP since the study researched KP and EC together; mortality data were available only for KP |
| BSI<br>R vs S  | 6                  | Kim BN, 2002         | Score               | -  | Mix  | 44 cases<br>118 controls  | -             | +                                       | ++            | ++                 | ++             | ++  | ++   | -   | +  | c.b.e  | -  | Mort. rate cases=23%<br>Mort. rate controls=20%   | Mean cases=39.6<br>controls=23.9  |
|                |                    |                      | Comments            | Retrospective cohort study                                       | HCA: 86.4% cases, 42.4% controls   |   |               |   |               |                    |                |   | not matched but controlled in univariate analyses  | not matched but controlled in univariate analyses for McCabe score                          | all BSI  | mortality in hospital                                |  |   |   |
| BSI<br>R vs S  | 7                  | Aniffin, 2000        | Score               | -  | c.b.e  | 16 cases<br>15 controls   | -             | -                                       | +             | -                  | ++             | c.b.e   | +  | -   | ++   | c.b.e  | ++   | Mort. rate cases=50%<br>Mort. rate controls=13%<br>OR=6.5, 95%CI(1.1-38.6)  |   |
|                |                    |                      | Comments            | Retrospective cohort study                                       | no information in the article  |   |               |   |               |                    |                | all patients are pediatric patients <12 years   | all patients were in pediatric oncology unit and had febrile neutropenia                       | no information  | not matched but controlled in univariate analyses for hematological malignancies | all BSI  | mortality in hospital  |   | the article defines the outcome as sepsis related mortality   |
| BSI<br>R vs S  | 8                  | Mosqueda-Gomez, 2008 | Score               | -  | Mix  | 17 cases<br>104 controls  | -             | -                                       | ++            | ++                 | ++             | +   | -  | -   | +  | c.b.e  | -  | Mort. rate cases=35%<br>Mort. rate controls=26.9%   | mean cases=20.9<br>controls=15.9  |
|                |                    |                      | Comments            | Retrospective case-control study                                 | HCA: 100% cases, 45.2% controls  |   |               |   |               |                    |                |   | not matched but controlled in univariate analyses, age was higher in controls                  | not matched but controlled in univariate analyses for McCabe score                          | all BSI  | mortality in hospital                                |  |   |   |
| BSI<br>R vs S  | 9                  | Szlajgyl, 2009       | Score               | -  | HCA  | 100 cases<br>100 controls   | -             | ++                                      | ++            | ++                 | ++             | ++  | -  | -   | -  | c.b.e  | ++   | a) Mort. rate cases=36%<br>Mort. rate controls=23%<br>OR=2.5, 95%CI(1.0-5.4)<br>b) Mort. rate cases=18%<br>Mort. rate controls=15%<br>OR=5, 95%CI(1.5-16.2) | median cases=10.5<br>controls=10  |
|                |                    |                      | Comments            | Retrospective cohort study                                       |  |   |               |   |               |                    |                |   | not matched but controlled in univariate analyses  | not matched but controlled in univariate analyses for McCabe score                          | all BSI  | mortality in hospital                                |  |   | all cause mortal; b)inf. related mort.  |
| BSI<br>R vs S  | 10                 | Pena, 2001           | Score               | +  | HCA  | 48 cases<br>43 controls   | -             | ++                                      | ++            | +                  | ++             | ++  | -  | +   | c.b.e  | -  | a) Mort. rate cases=32%<br>Mort. rate controls=24%<br>b) Mort. rate cases=16%<br>Mort. rate controls=14% |   |   |
|                |                    |                      | Comments            | Prospective cohort study   |  |   |               |   |               |                    |                | patients were part of an outbreak of ESBL KP  | not matched but controlled in univariate analyses  | not matched but controlled in univariate analyses for McCabe score and main diseases        | all BSI  | mortality in hospital                                |  |   | a)overall mortality<br>b)attributable mortality   |
| BSI<br>R vs S  | 11                 | Paterson, 2004       | Score               | +  | HCA  | 78 cases<br>175 controls  | -             | c.b.e                                   | ++            | ++                 | ++             | ++  | -  | -   | -  | -  | -  | Mort. rate cases=27%<br>Mort. rate controls=23%   | before isolation mean±SD cases=36.3±5.4<br>controls=19.9±1.9  |
|                |                    |                      | Comments            | International prospective study                                  |  |   |               |   |               |                    |                | different countries: South Africa, Taiwan, Australia, Argentina, the United States, Belgium, and Turkey | not matched but controlled in univariate analyses  | not matched but controlled in univariate analyses   | all BSI  | 14 days  |  |   |   |
| BSI<br>R vs S  | 12                 | Tuon, 2010           | Score               | -  | c.b.e  | 83 cases<br>41 controls   | -             | -                                       | ++            | ++                 | ++             | +   | +  | -   | +  | ++   | -  | Mort. rate cases=49.2%<br>Mort. rate controls=41.9%   | Mean ± SD cases=52.2 ± 39.6<br>controls=36.0 ± 29.4   |
|                |                    |                      | Comments            | Retrospective cohort study                                       | no information in the article  |   |               |   |               |                    |                | >12 years   | not matched but controlled in univariate analyses for age, gender was not equally distributed  | not matched but controlled in univariate analyses for McCabe score                          | all BSI  | 30 days  |  |   |   |
| BSI<br>R vs S  | 13                 | Lee, 2011            | Score               | -  | CA   | 33 cases<br>219 controls  | -             | +                                       | ++            | +                  | ++             | ++  | ++   | -   | +  | c.b.e  | -  | Mort. rate cases=12.1%<br>Mort. rate controls=16%   | Mean ± SD cases=26.5 ± 39.0<br>controls=19.9 ± 42.4   |
|                |                    |                      | Comments            | Retrospective case-control study                                 | community onset infection HCA: 75.8% cases, 56.2% controls                     | community-onset bacteremia  |               |   |               |                    |                | patients from Emergency department, with community onset infection                                      | not matched but controlled in univariate analyses  | not matched but controlled in univariate analyses for McCabe score and main diseases        | all BSI  | mortality in hospital                                |  |   |   |
| UTI<br>R vs S  | 1                  | Brizendine, 2015     | Score               | -  | HCA  | 22 cases<br>64 controls   | -             | +                                       | ++            | -                  | ++             | +   | +  | -   | +  | c.b.e  | -  | Mort. cases=18%<br>Mort. Contr.=2%  | Prior to UTI Median (IQR) cases=8(1-14)<br>controls=1(1-4)  |
| UTI<br>R vs S  | 1                  | Loh, 2006            | Score               | -  | Mix  | 47 cases<br>394 controls  | -             | -                                       | ++            | ++                 | ++             | ++  | ++   | -   | +  | c.b.e  | -  | Mort. rate cases=21.3%<br>Mort. rate controls=12.4%   | Median (IQR) cases=14(9-32)<br>controls=5(3-10)   |
| UTI<br>R vs S  | 1                  | Gomes, 2006          | Score               | -  | HCA  | 68 cases<br>75 controls   | ++            | -                                       | ++            | ++                 | ++             | -   | -  | -   | +  | c.b.e  | -  | Mort. rate cases=20.6%<br>Mort. rate controls=21.3%   | no data   |
| UTI<br>R vs S  | 2                  | Lin, 2003            | Score               | +  | Mix  | 43 cases<br>86 controls   | -             | +                                       | ++            | ++                 | ++             | +   | ++   | ++  | +  | c.b.e  | -  | Mort. rate cases=27.9%<br>Mort. rate controls=20.9%   | mean(range) cases=45 (0-143)<br>controls=18 (0-82)  |
| UTI<br>R vs S  | 3                  | Kuo, 2007            | Score               | -  | Mix  | 54 cases<br>54 controls   | -             | +                                       | +             | +                  | ++             | ++  | -  | ++  | ++   | ++   | -  | Mort. rate cases=15%<br>Mort. rate controls=13%   | mean(range) cases=45 (0-143)<br>controls=18 (0-82)  |
| UTI<br>R vs S  | 4                  | Chiu, 2005           | Score               | -  | HCA  | 15 cases<br>16 controls   | -             | +                                       | +             | +                  | ++             | +   | c.b.e  | c.be  | ++   | c.b.e  | c.b.e  | Mort. rate cases=20%<br>Mort. rate controls=12.5%   | no data   |
| UTI<br>R vs S  | 5                  | Huang, 2007          | Score               | +  | HCA  | 19 cases<br>12 controls   | -             | -                                       | +             | +                  | ++             | c.b.e   | -  | -   | ++   | ++   | c.b.e  | Mort. rate cases=10.5%<br>Mort. rate controls=0%  | no data   |
| UTI<br>R vs S  | 6                  | BARF, 2002           | Score               | -  | Mix  | 9 cases<br>9 controls   | -             | +                                       | ++            | ++                 | ++             | +   | ++   | ++  | -  | c.b.e  | -  | Mort. rate cases=44%<br>Mort. rate controls=33%   | median: cases=20<br>controls=33.5   |

**Sample size** N refers to total number of cases and controls (no score)  
**Calculation a priori:** ++ if performed (e.g. based on expected prevalence or on literature data) or the study refers to large national surveys; - if not performed  
**Study type:** ++ matched cohort or case-control studies; + prospective cohort or case-control studies; - retrospective database studies  
**Infection type** HCA: health-care associated; CA: community associated; Mix: health-care and community associated together  
**Representativeness** **Geographical:** ++ if the study was conducted in an EU/EEA setting; + if the study was conducted in high-income country (ref. World bank); - if the study was not conducted in an EU/EEA or high-income country setting  
**Demographical:** ++ if the study population represents all age groups; + if the study population represents selected age-specific groups (e.g. elderly, infants); - if the study population represents a selected sex category and age-specific groups  
**Clinical:** ++ if the study population represents the overall hospital population; + if the study population partially represents the hospital population; - if the study population represents a disease-specific population (e.g. liver transplanted patients, cancer patients, etc.)  
**Exclusion/inclusion criteria:** ++ if the same exclusion/inclusion criteria were adopted for both cases and controls; + if some (but not all) exclusion/inclusion criteria were adopted for both cases and controls; - if exclusion/inclusion criteria were different in cases and controls  
**Matching or controlling for confounders** **Demographics:** ++ if performed for age and sex; + if performed only for age or only for sex; - if not performed at all  
**Underlying disease:** ++ if performed for two or more criteria (e.g. comorbidity score, McCabe score, severity index, n. comorbidities, allergy, immunosuppression status, prior hospitalisation etc.); + if performed for only one criteria; - if not performed at all  
**Infection site:** ++ if performed; - if not performed  
**Hospital and unit/ward:** ++ if same hospital and same unit/ward; + if same hospital but different unit/ward; - if not same hospital and/or not same unit/ward  
**Follow-up:** ++ if ≥ 28 days; - if < 28 days  
**Risk difference** **Statistically significant outcome results:** ++ if results and 95% CI are statistically significant; - if results and 95% CI are not statistically significant  
**Case fatality and LOS:** refer to risk difference estimates in cases and controls (no score)

|        |  |
|--------|--|
| ++     | Matches completely/ is completely fulfilled                                      |
| +      | Matches incompletely but sufficiently/ is only partly but sufficiently fulfilled |
| -      | Does not match or matches insufficiently/ is insufficiently fulfilled            |
| c.b.e. | Cannot be evaluated  |

| CRKP Checklist for the evaluation of the most relevant studies for building antimicrobial resistance (AMR) outcome trees, healthcare-associated infection (HAI) attributable case fatality and attributable length-of-stay (LOS) |                    |  |                                    |  |  |  |                                   |   |   |   |   |   |  |  |   |   |  |   |  |
|--|--------------------|--|------------------------------------|--|--|--|-----------------------------------|---|---|---|---|---|--|--|---|---|--|---|--|
| No   | Study              | Study type   | Infection type                     | Sample size  |  | Representativeness   |                                   |   | Matching or controlling for confounders                               |   |   |   |  |  | Risk difference                             |   |  |   |  |
|  |                    |  |                                    | N (cases/controls)   | calculation a priori   | Geographical   | Demographical                     | Clinical  | Exclusion/inclusion criteria  | Demographics  | Underlying disease  | Infection site  | Hospital and unit/ward   | Follow-up  | Statistically significant outcome results   | Case fatality   | LOS  |   |  |
|  | First author, year |  | HCA; CA; Mix; c.b.e                |  | □ ++; □ +; □ -; □ c.b.e  | □ ++; □ +; □ -; □ c.b.e  | □ ++; □ +; □ -; □ c.b.e           | □ ++; □ +; □ -; □ c.b.e                         | □ ++; □ +; □ -; □ c.b.e   | □ ++; □ +; □ -; □ c.b.e                               | □ ++; □ +; □ -; □ c.b.e   | □ ++; □ +; □ -; □ c.b.e   | □ ++; □ +; □ -; □ c.b.e  | □ ++; □ +; □ -; □ c.b.e  | □ ++; □ +; □ -; □ c.b.e                     | □ ++; □ +; □ -; □ c.b.e   | □ ++; □ +; □ -; □ c.b.e  |   |  |
| BSI R vs NI  | 1                  | Borer, 2009  | Score                              | ++   | c.b.e  | 32 cases<br>32 controls  | -                                 | +   | ++  | ++  | ++  | ++  | ++   | -  | +   | c.b.e   | ++   | Mort. rate cases=71.9%<br>Mort. rate controls=21.9%<br>RR=3.3; 95%CI(2.9-28.5)  | median:<br>cases=21<br>controls=18   |
|  |                    | Comments   | Matched retrospective study        | no information in the article  | controls had an infectious disease but not BSI   |  |                                   |   |   |   |   |   |  | BSI vs NI (without BSI)  | mortality in hospital                       |   |  |   |  |
|  | 2                  | Gallagher, 2014  | Score                              | ++   | c.b.e  | 43 cases<br>154 controls   | -                                 | +   | ++  | ++  | ++  | -   | -  | -  | ++  | c.b.e   | ++   | Mort. cases= 45%<br>Mort. contr.= 18%<br>OR=3.8; 95%CI(1.4-9.9)   | mean:<br>cases=54<br>controls=19   |
| Comments   |                    | Matched Case-control study (matched only by month/year and unit) | no information in the article      |  |  |  |                                   |   |   |   | no univariate analyses  | no univariate analyses  | BSI vs NI  | mortality in hospital  |   |   |  |   |  |
| 3  | Mouloudi, 2014     | Score  | ++                                 | HCA  | 17 cases<br>34 controls  | -  | ++                                | ++  | -   | ++  | ++  | ++  | -  | ++   | c.b.e                                       | c.b.e   | Mort. cases=82.7%<br>Mort. contr.=32%  | in ICU<br>median (range):<br>cases=28(10-64)<br>controls=no info  |  |
|  |                    | Comments   | Observational matched cohort study |  |  |  |                                   |   | patients with liver transplant in ICU                                 | patients with liver transplant in ICU                 | not matched but controlled in univariate analyses   | not matched but controlled in univariate analyses for main indicators   | BSI vs NI  | ICU  | mortality in hospital                       | no information  |  |   |  |
| BSI R vs S   | 1                  | Falagas, 2014  | Score                              | -  | c.b.e  | 985 patients   | -                                 | c.b.e   | ++  | ++  | ++  | c.b.e   | c.b.e  | -  | -   | c.b.e   | ++   | Attrib. mort.= 26-44%<br>in 7 studies<br>(3) and (-4)% in 2 remaining studies<br>RR=2.05; 95%CI(1.56-2.69)*<br>RR 2.19; 95%CI(1.82-2.63)**<br>RR=1.46; 95%CI(0.47-4.49)***                              | no data  |
|  |                    |  | Comments                           | Review Meta-analysis (on Enterobacteriaceae, but 8/9 studies)                        | no information in the article  |  |                                   | Articles from different countries               |   | the same referred to cases and controls of each study |   | different in the different studies  | different in the different studies   | 6 studies were on BSI, the other 3 were on mixed site of infection | different in different studies              | only RR* and RR**   |  | * referred to all 9 studies<br>** only 6 BSI studies<br>*** remaining 3 (not BSI/mixed site of infection) studies   |  |
|  | 2                  | Mouloudi, 2010   | Score                              | +  | HCA  | 37 cases<br>22 controls  | -                                 | ++  | ++  | +   | ++  | ++  | ++   | -  | ++  | c.b.e   | c.b.e  | a) Mort. cases= 56.8%<br>Mort. contr.= 41%<br>b) Mort. cases= 56.8%<br>Mort. contr.= 41%<br>c) Mort. cases= 27%<br>Mort. contr.= 14%  | median(range):<br>total=26 (8-90) in ICU                                       |
|  |                    |  | Comments                           | Prospective nested case-control study  |  | cases were all CRKP, 18 metallo-β-lactamase KP and 17 carbapenemase-producing KP. The mortality for data were estimated together |                                   |   |   | ICU patient   | not matched but controlled in univariate analyses   | not matched but controlled in univariate analyses for main diseases   |  | all BSI  | mortality in hospital                       | no information  |  | a) mortality in ICU<br>b) mortality in hospital<br>c) attributable mortality (within 24h from infection or with infection symptoms despite appropriate therapy)<br>Mort. cases= 46%<br>Mort. contr.= 0% |  |
|  | 3                  | Simkins, 2014  | Score                              | -  | c.b.e  | 13 cases<br>39 controls  | -                                 | +   | +   | +   | +   | +   | +  | -  | +   | c.b.e   | +  | Mort. cases= 46%<br>Mort. contr.= 0%  | no data  |
|  |                    |  | Comments                           | Case-control study   | no information in the article  |  |                                   |   |   |   |   |   |  |  |   | 6.5 months  |  |   |  |
|  | 4                  | Vale, 2013   | Score                              | -  | Mix  | c.b.e  | -                                 | c.b.e   | ++  | ++  | NA  | c.b.e   | c.b.e  | -  | NA  | c.b.e   | c.b.e  | Crude mortality rates =20-70%<br>Attrib. mort. patients:<br>-hematologic=75%<br>-ICU=11%<br>-transplant=7%<br>-LIC=5%<br>-medicine=2%<br>-surgery=2%  | median time in developing CRKP infections in hospital (range): cases=14(0-152) |
| Comments   |                    |  | Review                             | the review does not pool the patients together, but considers every study separately |  |  | Articles from different countries |   |   |   | stratified with different results   | stratified with different results   | all BSI  | different in different studies                                     |   |   |  |   |  |
| 5  | Hussein, 2013      | Score  | -                                  | HCA  | 103 cases<br>214 controls  | -  | +                                 | +   | ++  | ++  | ++  | -   | -  | +  | ++  | ++  | Mort. cases= 43.7%<br>Mort. contr.= 29%  | median (range):<br>cases=17(1-125)<br>controls=12(1-202)  |  |
|  |                    | Comments   | Retrospective case-control study   |  | all patients had health-care associated infection  |  |                                   |   |   |   | not matched but controlled in univariate analyses   |   | all BSI  | 30 days  |   |   |  |   |  |
| 6  | Ben-David, 2012    | Score  | -                                  | Mix  | 42 cases<br>85 controls  | -  | +                                 | ++  | ++  | ++  | ++  | ++  | -  | +  | c.b.e                                       | ++  | a) Mort. cases=69%<br>Mort. contr.=24%<br>b) Mort. cases=48%<br>Mort. contr.=17%                                   | mean LOS before infection detection<br>±SD: survivors=25±5<br>deceased=27±37  |  |
|  |                    | Comments   | Retrospective cohort study         | HCA: 100% cases, 79% controls  |  |  |                                   |   |   |   | not matched but controlled in univariate analyses   | not matched but controlled in univariate analyses for Charlson's score, not other diseases                    | all BSI  | mortality in hospital  |   |   | in hospital mortality<br>b)infection related mortality   |   |  |
| 7  | Daikos, 2009       | Score  | +                                  | c.b.e  | 14 cases<br>148 controls   | -  | ++                                | ++  | ++  | ++  | +   | -   | -  | -  | -   | -   | Mort. cases= 42.8%<br>Mort. contr.= 16.9%<br>OR=3.95; 95%CI(0.94-16.6)   | mean LOS before bacteraemia ±SD:<br>both groups=25.85 ± 37.87   |  |
|  |                    | Comments   | Prospective observational study    | no information in the article  |  |  |                                   |   |   |   | not matched but controlled in univariate analyses for gender, age higher in controls      |   | all BSI  | 2 hospitals  | 14 days                                     |   |  |   |  |
| UTI R vs S   | 1                  | Brizendine, 2015   | Score                              | -  | c.b.e  | 22 cases<br>64 controls  | -                                 | +   | ++  | -   | ++  | ++  | +  | +  | c.b.e                                       | c.b.e   | Mort. cases=18%<br>Mort. contr.=2%   | median:<br>cases=7<br>controls=1  |  |
|  |                    |  | Comments                           | Retrospective cohort study   | no information in the article  |  |                                   |   | all patients had solid organ transplant                               |   |   | not matched but controlled in univariate analyses   | all patients had solid organ transplant, no other comorbidities considered | all UTI  | mortality in hospital                       | no information  |  |   |  |
|  | 2                  | Pouch, 2015  | Score                              | -  | HCA  | 20 cases<br>80 controls  | -                                 | +   | ++  | -   | ++  | ++  | -  | -  | +   | c.b.e   | ++   | Mort. cases=30%<br>Mort. contr.=10%<br>HR=3.0; 95%CI(1.0-9.0)   | median(OR):<br>cases=17(9-43)<br>controls=7(5-10)                              |
| Comments   |                    |  | Retrospective case-control study   | not explicitly said in the article, but very specific patients                       |  |  |                                   | all patients had solid kidney transplant        |   |   | not matched but controlled in univariate analyses   |   | all UTI  | not defined  |   |   |  |   |  |
| 3  | Shilo, 2013        | Score  | -                                  | c.b.e  | 135 cases<br>127 controls  | ++   | +                                 | ++  | ++  | ++  | ++  | ++  | -  | +  | c.b.e                                       | -   | Mort. cases=29%<br>Mort. contr.=25%  | mean±SD<br>cases=29.33<br>controls=22±28  |  |
|  |                    | Comments   | Retrospective case-control study   | no information in the article  | cases defined as bacteremia, since UTI relates with asymptomatic while bacteremia not always |  |                                   |   |   |   | not matched but controlled in univariate analyses   | not matched but controlled in univariate analyses for main diseases   | all bacteremia   | mortality in hospital  |   |   |  |   |  |
| Mixed inf. site R vs NI  | 1                  | Giannella, 2014  | Score                              | ++   | HCA  | 10 cases<br>20 controls  | -                                 | ++  | ++  | -   | ++  | ++  | ++   | +  | ++  | -   | a) Mort. cases=0%<br>Mort. Contr.=5%<br>b) Mort. cases=0%<br>Mort. contr.=15%                                      | median (range):<br>cases=16(14-27)<br>controls=20(15-62)  |  |
|  |                    |  | Comments                           | Matched case-control study   | not explicitly said in the article, but very specific patients                               | the cases were selected when colonized, though all of them after developed BSI   |                                   |   | all patients had liver transplant                                     |   |   | not matched but controlled in univariate analyses   | not matched but controlled in univariate analyses                          | all cases had positive rectal swabs initially and BSI's after      | a)30 days<br>b)60 days                      |   | a)30 days<br>b)60 days   |   |  |
|  | 2                  | Luebbert, 2014   | Score                              | -  | HCA  | 9 cases<br>18 controls   | -                                 | ++  | ++  | -   | ++  | ++  | -  | +  | ++  | ++  | Mort. cases=78%<br>Mort. contr.=11%  | cases=60<br>controls=32   |  |
|  |                    |  | Comments                           | Retrospective case-control study   | not explicitly said in the article, but very specific patients                               |  |                                   | all patients had liver transplant               |   |   |   |   |  | R vs NI  | 3 months from last case                     |   |  |   |  |
|  | 3                  | Nouvenne, 2014   | Score                              | -  | c.b.e  | 133 cases<br>(93 colonized,<br>40infected)<br>400 controls   | -                                 | ++  | ++  | ++  | +   | ++  | -  | ++   | c.b.e                                       | -   | Mort. cases =21.8%<br>(Mort. Infected)=47.5%<br>Mort. Colonized=10.7%<br>Mort. contr. =15%                         | mean±SD<br>cases=29.33<br>controls=18±12  |  |
|  |                    |  | Comments                           | Retrospective cross-sectional study  | no information in the article  |  |                                   |   | cases were part of an outbreak, while controls were randomly selected |   |   | not matched but controlled in univariate analyses   |  | R vs NI  | mortality in hospital                       | refers only to the comparison of all cases (infected+colonized) with controls   |  |   |  |
|  | 4                  | Bleumin, 2012  | Score                              | +  | HCA  | 43 cases<br>150 controls   | -                                 | +   | ++  | -   | ++  | +   | ++   | -  | ++  | c.b.e   | ++   | Mort. cases= 88%<br>Mort. contr.= 52%<br>aHR=0.9; 95%CI(0.3-2.11.0)   | no data  |
|  |                    |  | Comments                           | Prospective nested case-control study  |  |  |                                   | all patients were chronic hemodialysis patients |   |   | not matched but controlled in univariate analyses for age, cases had more female patients | not matched but controlled in univariate analyses for main diseases, differences in central catheter presence |  | R vs NI  | study period                                |   |  |   |  |
| 5  | Debby, 2012        | Score  | +                                  | HCA  | 48 cases<br>132 controls   | -  | +                                 | ++  | +   | ++  | ++  | ++  | -  | ++   | c.b.e                                       | -   | Mort. cases=45.8%<br>Mort. contr.=38.6%  | mean±SD<br>cases=6.06±1.23<br>controls=8.39 ±1.49   |  |
|  |                    | Comments   | Prospective cohort study           |  | all cases were detected with rectal swab analyses, but developed BSI, pneumonia, etc         |  |                                   | ICU patients                                    |   |   | not matched but controlled in univariate analyses   | not matched but controlled in univariate analyses for main diseases   | R vs NI  | mortality in hospital  |   |   |  |   |  |
| 6  | Schwaber, 2008     | Score  | -                                  | HCA  | 48 CRKP<br>56 CSKP<br>59 controls  | -  | +                                 | ++  | ++  | ++  | ++  | -   | +  | c.b.e  | ++  | Mort. rate resistant=44%<br>Mort. rate sensitive=12.5%<br>Mort. rate NI=2%<br>R vs S: OR=5.4;<br>95%CI(1.7-17.1)<br>R vs NI: OR=6.7;<br>95%CI(2.4-18.8) | median (OR):<br>cases=19 (9-38)<br>controls=2 (1-4)  |   |  |
|  |                    | Comments   | Retrospective case-control study   |  |  |  |                                   |   |   |   | not matched but controlled in univariate analyses   |   |  | mortality in hospital  |   |   |  |   |  |
| 7  | Pereira, 2015      | Score  | -                                  | HCA  | 20 CRKP<br>36 CSKP<br>248 controls   | -  | +                                 | ++  | -   | ++  | ++  | -   | +  | ++   | ++  | ++  | Mort. rate resistant=45%<br>Mort. rate sensitive=28%<br>Mort. rate NI=7%<br>R vs NI: HR=6.92;<br>95%CI(3.24-14.79) | Median (range):<br>cases=40(23-82)<br>controls=12 (9-21)  |  |
|  |                    | Comments   | Retrospective cohort study         | not explicitly said in the article, but very specific patients                       | the results are presented for R vs (S+NI)  |  |                                   | all patients had liver transplant               |   |   | not matched but controlled in univariate analyses   |   |  | 1 year from transplant   | HR, no data on mortality rates              |   | Mortality rates extracted from survival analyses   |   |  |
| 8  | Kofteridis, 2014   | Score  | -                                  | c.b.e  | 83 resistant<br>161 NI   | -  | ++                                | ++  | ++  | ++  | +   | -   | +  | c.b.e  | ++  | Mort. rate resistant=27%<br>Mort. rate sensitive=15%<br>Mort. rate NI=4%  | no data  |   |  |
|  |                    | Comments   | Case-control study                 | no information in the article  |  |  |                                   |   |   |   | not matched but controlled in univariate analyses for age                                 |   |  | not defined  | significant R vs NI, not significant R vs S |   |  |   |  |
| Mixed inf. site R vs S   | 1                  | Candevir Ulu, 2015   | Score                              | -  | HCA  | 47 cases<br>51 controls  | -                                 | -   | ++  | ++  | ++  | +   | -  | +  | c.b.e                                       | -   | Mortality cases=44.7%<br>Mortality contr.=51%  | mean:<br>cases=37.3<br>controls=29.94<br>median:<br>cases=19<br>controls=11   |  |
|  |                    |  | Comments                           | Retrospective cohort study   |  |  |                                   |   |   |   | not matched but controlled in univariate analyses for age                                 |   |  |  | mortality in hospital                       |   |  |   |  |
| 2  | Dizbay, 2014       | Score  | -                                  | HCA  | 42 cases<br>798 controls   | -  | -                                 | ++  | ++  | ++  | ++  | -   | +  | c.b.e  | ++  | Mortality cases=57.1%<br>Mortality contr.=27.4%   | mean<br>cases=38.27<br>controls=28.17  |   |  |
|  |                    | Comments   | Retrospective study                |  |  |  |                                   |   |   |   | not matched but controlled in univariate analyses   |   |  | not defined  |   |   |  |   |  |

|   |                   |          |   |                               |   |    |    |    |    |    |  |   |    |    |                       |                      |   |  |   |
|---|-------------------|----------|---|-------------------------------|---|----|----|----|----|----|--|---|----|----|-----------------------|----------------------|---|--|---|
| 3 | Hoxha, 2016       | Score    | ++  | c.b.e                         | 49 cases<br>49 controls   | ++ | ++ | ++ | ++ | ++ | ++   | ++  | ++ | -  | ++                    | ++                   | a) Attrib. mort.= 16%<br>b) Attrib. mort.= 41%<br>mRR=3.0; 95%CI(1.3-7.1) | no data  |   |
|   |                   | Comments | Matched cohort study                        | no information in the article |   |    |    |    |    |    | Matched for age and controlled in univariate analyses for gender   | not matched but controlled in univariate analyses for Charlson index and SAPS 2 score                           |    |    | a)6 days<br>b)30 days |                      | a)6 days<br>b)30 days   |  |   |
| 4 | Jiao, 2015        | Score    | -   | HCA                           | 30 cases<br>30 controls   | -  | -  | ++ | ++ | ++ | ++   | -   | -  | +  | c.b.e                 | c.b.e                | Mort. cases=33.6%<br>Mort. contr.=16.6%                                   | mean: cases=33.8<br>controls=18  |   |
|   |                   | Comments | Retrospective case-control study            |                               |   |    |    |    |    |    | Matched for age and controlled in univariate analyses for gender   |   |    |    | mortality in hospital | no information       |   |  |   |
| 5 | Patel, 2008       | Score    | ++  | c.b.e                         | 99 cases<br>99 controls   | -  | +  | ++ | ++ | ++ | ++   | ++  | ++ | +  | c.b.e                 | ++                   | Mort. cases=48%<br>Mort. contr.=26%<br>OR=4.69; 95%CI(1.9-11.58)          | mean±SD cases=25.19±24.9<br>controls=6.44±10.1<br>median: cases=21<br>controls=1   |   |
|   |                   | Comments | Matched case-control study                  | no information in the article |   |    |    |    |    |    | not matched but controlled in univariate analyses  | not matched but controlled in univariate analyses for main diseases   |    |    | mortality in hospital |                      |   |  |   |
| 6 | Correa, 2013      | Score    | ++  | HCA                           | 20 cases<br>40 controls   | -  | -  | ++ | ++ | ++ | ++   | +   | ++ | ++ | c.b.e                 | -                    | Mort. cases=50%<br>Mort. contr.=27.5%                                     | mean: cases=45.5<br>controls=27  |   |
|   |                   | Comments | Matched case-control study                  |                               | all HCA infections  |    |    |    |    |    | not matched but controlled in univariate analyses  | not matched but controlled in univariate analyses for MC Cabe score, APACHE II score at admission was different |    |    | mortality in hospital |                      |   |  |   |
| 7 | CDC Atlanta, 2011 | Score    | ++  | c.b.e                         | 19 cases<br>38 controls   | -  | +  | ++ | ++ | ++ | +  | ++  | -  | -  | c.b.e                 | c.b.e                | Mortality cases=6%<br>Mortality controls=8%                               | mean: cases=11.4<br>controls=7.4   |   |
|   |                   | Comments | Matched case-control study                  | no information in the article | outbreak patients   |    |    |    |    |    | matched for age  | not matched but controlled in univariate analyses for Charlson index  |    |    | mortality in hospital | no information       |   |  |   |
| 8 | Falagas, 2007     | Score    | ++  | HCA                           | 53 cases<br>53 controls   | -  | ++ | ++ | ++ | ++ | ++   | -   | ++ | -  | c.b.e                 | -                    | Mortality cases=30.1%<br>Mortality controls=33.9%                         | mean±SD cases=21.4±23.9<br>contr.=15.3±19.9  |   |
|   |                   | Comments | Matched case-control study                  |                               |   |    |    |    |    |    | matched for age, and controlled for gender in univariate analyses  |   |    |    | mortality in hospital |                      |   |  |   |
| 9 | Hauk, 2016        | Score    | -   | c.b.e                         | 260 cases:<br>(60 BSI, 49 pneumonia,<br>121 UTI)<br>223 controls* | -  | +  | ++ | ++ | ++ | ++   | ++  | ++ | NA | -                     | c.b.e                | ++  | Mort. rate BSI=38%<br>aHR=2.59; 95%CI(1.52-4.50)<br>Mort. rate Pneu=34%<br>aHR=3.44; 95%CI(1.80-6.48)<br>Mort. rate UTI=7%<br>aHR=0.68; 95%CI(0.30-1.45)<br>Mort. rate contr.=9% | median (IQR) BSI=14 (9-24)<br>Pneu=19 (10-30)<br>UTI=10 (6-17)<br>controls=9 (5-16) |
|   |                   | Comments | Prospective multicenter observational study | no information in the article | R vs CRKP urinary colonization                                    |    |    |    |    |    | not matched but controlled in univariate analyses for age and gender (Pneu & UTI). For BSI were both different | not matched but controlled in univariate analyses for Charlson index and main diseases                          |    |    | mortality in hospital | aHR BSI and aHR Pneu |   |  |   |

Sample size N refers to total number of cases and controls (no score)  
**Calculation a priori:** ++ if performed (e.g. based on expected prevalence or on literature data) or the study refers to large national surveys; - if not performed

**Study type:** ++ matched cohort or case-control studies; + prospective cohort or case-control studies; - retrospective database studies

**Infection type:** HCA: health-care associated; CA: community associated; MC: health-care and community associated together

**Geographical:** ++ if the study was conducted in an EU/EEA setting; + if the study was conducted in high-income country (ref. World Bank); - if the study was not conducted in an EU/EEA or high-income country setting

**Demographic:** ++ if the study population represents all age groups; + if the study population represents selected age-specific groups (e.g. elderly, infants); - if the study population represents a selected sex category and age-specific groups

**Clinical:** ++ if the study population represents the overall hospital population; + if the study population partially represents the hospital population; - if the study population represents a disease-specific population (e.g. liver transplanted patients, cancer patients, etc.)

**Exclusion/inclusion criteria:** ++ if the same exclusion/inclusion criteria were adopted for both cases and controls; + if some (but not all) exclusion/inclusion criteria were adopted for both cases and controls; - if exclusion/inclusion criteria were different in cases and controls

**Demographics:** ++ if performed for age and sex; + if performed only for age or only for sex; - if not performed at all

**Matching or controlling for Underlying disease:** ++ if performed for two or more criteria (e.g. comorbidity score, McCabe score, severity index, n. comorbidities, allergy, immunosuppression status, prior hospitalisation etc.); + if performed for only one criteria; - if not performed at all

**Infection site:** ++ if performed; - if not performed

**Hospital and unit/ward:** ++ if same hospital and same unit/ward; + if same hospital but different unit/ward; - if not same hospital and/or not same unit/ward

**Follow-up:** ++ if ≥ 28 days; - if < 28 days

**Statistically significant outcome results:** ++ if results and 95%CI are statistically significant; - if results and 95%CI are not statistically significant

**Case fatality and LOS** refer to risk difference estimates in cases and controls (no score)

Scoring table

|        |   |
|--------|---|
| ++     | Matches completely/ is completely fulfilled                                       |
| +      | Matches incompletely but sufficiently/ is only partly/ but sufficiently fulfilled |
| -      | Does not match or matches insufficiently/ is insufficiently fulfilled             |
| c.b.e. | Cannot be evaluated   |

| Nr                     | First author, year | Study type     | Infection type                  | Sample size                    |                             | Representativeness |               |  | Matching or controlling for confounders  |  |  |                       |                        | Risk difference       |   |   |   |
|------------------------|--------------------|----------------|---------------------------------|--------------------------------|-----------------------------|--------------------|---------------|--|--|--|--|-----------------------|------------------------|-----------------------|---|---|---|
|                        |                    |                |                                 | N (cases/controls)             | calculation a priori        | Geographical       | Demographical | Clinical   | Exclusion/inclusion criteria   | Demographics   | Underlying disease   | Infection site        | Hospital and unit/ward | Follow-up             | Statistically significant outcome results | Case fatality   | LOS   |
| Mixed inf. site R vs S | 1                  | Marchaim, 2010 | HCA                             | 5 cases<br>60 controls         | -                           | +                  | ++            | ++   | ++   | -  | -  | -                     | -                      | c.b.e.                | -   | Mort. rate cases=40%<br>Mort. rate controls=26%   | Mean±SD<br>Cases=33±23<br>Controls=30±23          |
|                        |                    |                |                                 | all patients were also CRKP    |                             |                    |               |  |  |  |  |                       | mortality in hospital  |                       |   |   |   |
|                        | 2                  | Zarkotou, 2010 | HCA                             | 13 cases<br>39 controls        | -                           | ++                 | ++            | ++   | ++   | +  | ++   | ++                    | ++                     | c.b.e.                | ++  | Mort. rate cases=69.2%<br>Mort. Rate controls=35.9%<br>Attribut. mort.=37.5% in both groups | Mean±SD<br>Cases=20.5±20.8<br>Controls= 16.4±12.3 |
|                        |                    |                |                                 | Matched Case Control Study     |                             |                    |               |  | not matched but controlled for age in univariate analyses. Gender is different               | not matched but controlled for main comorbidities and there was no difference                |  |                       |                        | mortality in hospital | difference in all cause mortality         | *not defined in the paper   |   |
| 3                      | Capone, 2013       | HCA            | 35 cases<br>62 controls         | -                              | ++                          | ++                 | ++            | ++   | ++   | c.b.e.   | c.b.e.   | c.b.e.                | c.b.e.                 | c.b.e.                | ++  | Mort. rate cases=40.6%<br>Mort. rate controls=20.3%   | not specific data                                 |
|                        |                    |                | Multicentre Prospective Study   |                                |                             |                    |               | study not specific for colistin resistance, only mortality data available for the two groups | study not specific for colistin resistance, only mortality data available for the two groups | study not specific for colistin resistance, only mortality data available for the two groups | study not specific for colistin resistance, only mortality data available for the two groups | mortality in hospital |                        |                       |   |   |   |
| 4                      | Rojas, 2016        | Mix            | 31 cases<br>215 controls        | -                              | +                           | ++                 | ++            | ++   | ++   | ++   | ++   | -                     | -                      | ++                    | ++  | Mort. rate cases=51%<br>Mort. rate controls=39%<br>aHR=3.48; 95%CI(1.77-6.57)               | Median(IQR)<br>Cases=8(5-12)<br>Controls=13(7-26) |
|                        |                    |                | Prospective nested cohort study | HCA; 32% cases<br>49% controls | all patients were also CRKP |                    |               |  |  | not matched but controlled in univariate analyses  | not matched but controlled for main comorbidities and Charlson's index                       |                       |                        | 30 days               |   |   |   |

**Sample size**  
N refers to total number of cases and controls (no were)  
**Calculation a priori:** ++ if performed (e.g. based on expected prevalence or on literature data) or the study refers to large national surveys; - if not performed

**Study type:** ++ matched cohort or case-control studies; + prospective cohort or case-control studies; - retrospective database studies  
**Infection type:** HCA: health-care associated; CA: community associated; Mix: health-care and community associated together

**Representativeness**  
**Geographical:** ++ if the study was conducted in an EU/EEA setting; + if the study was conducted in high-income country (ref. World bank); - if the study was not conducted in an EU/EEA or high-income country setting  
**Demographical:** ++ if the study population represents all age groups; + if the study population represents selected age-specific groups (e.g. elderly, infants); - if the study population represents a selected sex category and age-specific groups  
**Clinical:** ++ if the study population represents the overall hospital population; + if the study population partially represents the hospital population; - if the study population represents a disease-specific population (e.g. liver transplanted patients, cancer patients, etc.)  
**Exclusion/inclusion criteria:** ++ if the same exclusion/inclusion criteria were adopted for both cases and controls; + if some (but not all) exclusion/inclusion criteria were adopted for both cases and controls; - if exclusion/inclusion criteria were different in cases and controls  
**Demographics:** ++ if performed for age and sex; + if performed only for age or only for sex; - if not performed at all

**Matching or controlling for confounders**  
**Underlying disease:** ++ if performed for two or more criteria (e.g. comorbidity score, McCabe score, severity index, n. comorbidities, allergy, immunosuppression status, prior hospitalisation etc.); + if performed for only one criteria; - if not performed at all  
**Infectious site:** ++ if performed; - if not performed  
**Hospital and unit/ward:** ++ if same hospital and same unit/ward; + if same hospital but different unit/ward; - if not same hospital and/or not same unit/ward  
**Follow-up:** ++ if ≥ 28 days; - if < 28 days

**Risk difference**  
**Statistically significant outcome results:** ++ if results and 95%CI are statistically significant; - if results and 95%CI are not statistically significant  
**Case fatality and LOS** refer to risk difference estimates in cases and controls (no score)

Scoring table

|        |   |
|--------|---|
| ++     | Matches completely/is completely fulfilled                                      |
| +      | Matches incompletely but sufficiently/is only partly but sufficiently fulfilled |
| -      | Does not match or matches insufficiently/is insufficiently fulfilled            |
| c.b.e. | Cannot be evaluated   |

| No | First author, year      | Study type | Infection type                             | Sample size   |   | Representativeness |                     |                     |                                      | Matching or controlling for confounders   |   |                     |                        |  | Statistically significant outcome results   | Risk difference   |  |   |
|----|-------------------------|------------|--|---|---|--------------------|---------------------|---------------------|--------------------------------------|---|---|---------------------|------------------------|--|---|---|--|---|
|    |                         |            |  | N (cases/controls)  | calculation a priori  | Geographical       | Demographical       | Clinical            | Exclusion/inclusion criteria         | Demographics  | Underlying disease  | Infection site      | Hospital and unit/ward | Follow-up  |   | Case fatality   | LOS  |   |
|    |                         |            | HCA; CA; Mix; c.b.e                        |   | 0++; 0+; 0; 0.c.b.e   | 0++; +; 0; 0.c.b.e | 0++; 0+; 0; 0.c.b.e | 0++; 0+; 0; 0.c.b.e | 0++; 0+; 0; 0.c.b.e                  | 0++; 0+; 0; 0.c.b.e   | 0++; 0+; 0; 0.c.b.e   | 0++; 0+; 0; 0.c.b.e | 0++; 0+; 0; 0.c.b.e    | 0++; 0+; 0; 0.c.b.e                                      | 0++; 0+; 0; 0.c.b.e   | %; RR; OR; aHR; etc   | (days)   |   |
| 1  | de Kraker, 2011         | Score      | ++   | Mix   | C1) 111 resistant<br>204 NI controls for resistant<br>C2) 1110 sensitive<br>2084 NI controls for sensitive      | -                  | ++                  | ++                  | ++                                   | ++  | ++  | -                   | -                      | ++   | ++  | C1: Mort. resist=32%<br>Mort. control=6%<br>OR=4.6, 95%CI(1.7-12.3)<br>C2: Mort. sensit=17%<br>Mort. control=7%<br>OR=1.9, 95%CI(1.4-2.5)<br>OR R vs S= 2.5, 95%CI(0.9-6.8)<br>C1: Mort. resist=36%<br>Mort. control=5%<br>HR=5.7, 95%CI(2.5-13.0)<br>C2: Mort. sensit=17%<br>Mort. control=7%<br>HR=2.0, 95%CI(1.5-2.5)<br>HR R vs S=2.9, 95%CI(1.2-6.9) | median (IQR)<br>C1: resist=12(6-25)<br>control=6(3-16)<br>C2: sensit=10(6-17)<br>control=7 (4-14)  |   |
|    |                         | Comments   | Prospective parallel matched double cohort | hospital onset of BSI: 57% resistant 26% sensitive                  | the study considered the patients as two cohorts, C1=R vs NI and C2=S vs NI                                     |                    |                     |                     |                                      | not matched but controlled in the univariate analyses. In the sensitive-control groups the age was higher in the cases. |   |                     | all BSI                |  | 30 days<br>b)hospital   |   |  |   |
| 1  | Anunatsiri, 2012        | Score      | -  | Mix   | 32 cases<br>113 controls  | -                  | -                   | ++                  | ++                                   | ++  | ++  | ++                  | -                      | +  | c.b.e   | ++  | Mort. cases=29%<br>Mort. controls= 11.5%   | prior bacteremia<br>median (range)<br>cases=4 (0-46)<br>controls=0 (0-82)   |
|    |                         | Comments   | Retrospective case-control study           | HCA: 76% cases, 26.5% controls<br>CA: 25% cases, 73.5% controls     |   | >15 years          |                     |                     |                                      | not matched but controlled in univariate analyses   | not matched but controlled in univariate analyses for main diseases and APACHE II score   |                     | all BSI                | mortality in hospital                                    |   |   |  |   |
| 2  | Apsamtharak, 2008       | Score      | -  | CA  | 24 cases<br>108 controls*   | -                  | -                   | ++                  | ++                                   | ++  | c.b.e   | c.b.e               | ++                     | ++   | c.b.e   | c.b.e   | Mort. cases=8%<br>Mort. controls= 15%*   | median (range);<br>cases=8 (4-15)<br>controls=3-15  |
|    |                         | Comments   | Retrospective case-control study           | all cases had community onset BSI                                   | *controls had EC or KP the study included EC and KP but it was possible to have the mortality only for EC cases |                    |                     |                     | the study results included EC and KP | the study results included EC and KP  |   |                     |                        | mortality in hospital                                    | the study results included EC and KP  |   |  | *controls had EC or KP  |
| 3  | Cormejo-Juarez, 2012    | Score      | -  | HCA   | 88 cases<br>88 controls   | -                  | -                   | -                   | -                                    | ++  | ++  | -                   | -                      | ++   | ++  | c.b.e   | a)Mort. cases=38.6%<br>Mort. controls=21.6%<br>b)Mort. cases=19.3%<br>Mort. controls= 25%  | difficult to interpret  |
|    |                         | Comments   | Retrospective case-control study           |   | the study started with 100 patients for each group, but 12 from each group were lost at follow-up               |                    |                     |                     |                                      | all patients had hematological malignancies   | not matched but controlled in univariate analyses   |                     | all BSI                | 60 days  | the results were presented separately for appropriate and inappropriate therapy. Here we pooled them. |   | a) death related to infection b) death not related to infection  |   |
| 4  | Courpon-Claudinon, 2011 | Score      | +  | Mix   | 39 cases<br>1012 controls   | -                  | ++                  | ++                  | ++                                   | ++  | +   | -                   | -                      | -  | c.b.e   | ++  | Mort. cases=30.8%<br>Mort. controls= 12.3%   | no data   |
|    |                         | Comments   | Prospective multi-centre study             | HCA: 23.1% cases, 19.1% controls<br>CA: 76.9% cases, 80.9% controls |   |                    |                     |                     |                                      | not matched but controlled and age is not significantly different, gender does  |   |                     | all BSI                | mortality in hospital                                    |   |   |  |   |
| 5  | Ortega, 2009            | Score      | +  | Mix   | 211 cases<br>3247 controls  | -                  | ++                  | ++                  | ++                                   | ++  | c.b.e   | c.b.e               | -                      | +  | ++  | c.b.e   | Mort. cases=15.6%<br>Mort. controls= 7.6%  | no data   |
|    |                         | Comments   | Prospective study                          | cases: 61% HCA, 39% CA controls: no specific info                   |   |                    |                     |                     |                                      | data on the ESBL-EC available only on supplementary tables which are inaccessible                                       | data on the ESBL-EC available only on supplementary tables which are inaccessible   |                     | all BSI                | a) 7 days<br>b) 30 days                                  | data on the ESBL-EC available only on supplementary tables which are inaccessible                     |   |  |   |
| 6  | Trecarichi, 2009        | Score      | -  | Mix   | 26 cases<br>36 controls   | -                  | ++                  | ++                  | -                                    | ++  | +   | -                   | -                      | ++   | ++  | ++  | Mort. cases=42.3%<br>Mort. controls= 5.6%<br>OR=8.84, 95%CI(1.48-52.91)  | no data   |
|    |                         | Comments   | Retrospective cohort                       | HCA: 96.1% cases, 75% controls<br>CA: 3.9% cases, 25% controls      |   |                    |                     |                     |                                      | not matched but controlled and gender is not significantly different, age is higher in cases                            | different type of hematological malignancies  |                     | all BSI                | 30 days  | OR  |   |  |   |
| 7  | Hsieh, 2010             | Score      | -  | CA  | 19 cases<br>385 controls  | -                  | +                   | ++                  | ++                                   | ++  | ++  | ++                  | -                      | +  | ++  | -   | Mort. cases=21.1%<br>Mort. controls= 12.2%   | mean (s.d);<br>cases=15.5(s4.5)<br>controls=6.1(s4.9)   |
|    |                         | Comments   | Retrospective cohort                       | community onset BSI   |   |                    |                     |                     |                                      | not matched but controlled in univariate analyses   | not matched but controlled in univariate analyses for main diseases   |                     | all BSI                | 30 days  |   |   |  |   |
| 8  | Tumbarello, 2010        | Score      | -  | Mix   | 37 cases<br>97 controls   | -                  | ++                  | ++                  | ++                                   | ++  | ++  | -                   | -                      | +  | ++  | ++  | Mort. cases=29.7%<br>Mort. controls= 6.1%<br>OR=4.43, 95%CI(2.46-7.95)   | mean (s.d)<br>cases=20(s17)<br>controls=13(s9)  |
|    |                         | Comments   | Retrospective cohort                       | HCA: 91.8% cases, 69% controls<br>CA: 8.2% cases, 30.9% controls    |   |                    |                     |                     |                                      | not matched but controlled in univariate analyses   | not matched but controlled in univariate analyses for APACHE II score. There are differences in solid tumors, more in controls            |                     | all BSI                | 21 days  | OR  |   |  |   |
| 9  | Gudiol, 2010            | Score      | +  | Mix   | 17 cases<br>118 controls  | -                  | ++                  | ++                  | -                                    | ++  | +   | ++                  | -                      | +  | ++*   | -   | a)Mort. cases=12%<br>Mort. controls= 8%<br>b)Mort. cases=35%<br>Mort. controls= 19%  | no data   |
|    |                         | Comments   | Prospective cohort                         | HCA: 94% cases, 88% controls  | hospitalized patients with cancer or hematological malignancies   |                    |                     |                     |                                      | not matched but controlled and age is not significantly different, gender does  | not matched but controlled for additional comorbidities   |                     | all BSI                | a) within 7 days<br>b) within 30 days                    |   | a) within 7 days<br>b) within 30 days   |  |   |
| 10 | Ho, 2002                | Score      | -  | Mix   | 50 cases<br>100 controls  | -                  | +                   | ++                  | ++                                   | ++  | ++  | -                   | -                      | +  | ++  | ++  | Mort. cases=18%<br>Mort. controls= 7%  | no data   |
|    |                         | Comments   | Retrospective case-control study           | HCA: 80% cases, 22.2% controls                                      |   |                    |                     |                     |                                      | not matched but controlled and age is not significantly different, gender does  |   |                     | all BSI                | within 30 days   |   |   |  |   |
| 11 | Rodriguez-Bano, 2010    | Score      | +  | CA  | 95 cases<br>188 controls  | -                  | ++                  | ++                  | ++                                   | ++  | ++  | -                   | -                      | -  | ++  | ++  | Mort. cases=17%<br>Mort. controls= 8%  | no data   |
|    |                         | Comments   | Prospective cohort                         | community onset BSI<br>HCA: 76% cases, 53% controls                 | patients with community onset BSI   |                    |                     |                     |                                      | not matched but controlled in univariate analyses   |   |                     | all BSI                | patients in different hospitals but matched for hospital | 14 days   |   |  |   |
| 12 | Kang, 2010              | Score      | -  | CA  | 82 case<br>783 controls   | -                  | +                   | ++                  | ++                                   | ++  | +   | -                   | -                      | +  | ++  | ++  | Mort. cases=15%<br>Mort. controls= 7.6%<br>OR=2.99, 95%CI(1.01-8.84)   | no data   |
|    |                         | Comments   | Retrospective cohort                       | community onset BSI<br>HCA: 36.6% cases, 15.7% controls             | patients with community onset BSI   |                    |                     |                     |                                      | not matched but controlled and age is not significantly different, gender does  |   |                     | all BSI                | 30 days  | OR  |   |  |   |
| 13 | Garcia-Hernandez, 2010  | Score      | c.b.e                                      | Mix   | 34 cases<br>119 controls  | -                  | ++                  | ++                  | ++                                   | ++  | ++  | -                   | -                      | +  | ++  | ++  | a)Mort. cases=35.5%<br>Mort. controls= 16.8%<br>b)Mort. cases=65%<br>Mort. controls= 9.2%  | mean (s.d)<br>cases=24.3(s22)<br>controls=20.9(s26.7)   |
|    |                         | Comments   | Retrospective and prospective cohort study | HCA: 47.1% cases, 44.5% controls<br>CA: 52.9% cases, 55.5% controls |   |                    |                     |                     |                                      | not matched but controlled in univariate analyses   |   |                     | all BSI                | 7 days   |   | a) within 72h<br>b)within 7 days  |  |   |
| 14 | Denis, 2015             | Score      | -  | Mix   | 41 cases<br>41 controls   | -                  | ++                  | ++                  | ++                                   | ++  | ++  | -                   | -                      | +  | ++  | -   | Mort. cases=30%<br>Mort. controls= 27%<br>OR=1.23, 95%CI(0.36-4.23)  | median (range)<br>cases=15 (10-21)<br>controls=11 (7-17)  |
|    |                         | Comments   | Retrospective study                        | HCA: 83% cases, 71% controls  |   |                    |                     |                     |                                      | not matched but controlled in univariate analyses   | not matched but controlled in univariate analyses for APACHE II score. There are differences in hematological malignancies, more in cases |                     | all BSI                | 30 days  |   |   |  |   |
| 15 | Ha, 2013                | Score      | -  | Mix   | 95 cases<br>255 controls  | -                  | +                   | ++                  | -                                    | ++  | +   | -                   | -                      | +  | ++  | ++  | Mort. cases=22.1%<br>Mort. controls= 12.2%<br>OR = 3.01, 95%CI(1.45-6.28)  | no data   |
|    |                         | Comments   | Retrospective cohort study                 | HCA: 85.3% cases, 66.3% controls<br>CA: 85.3% cases, 33.7% controls |   |                    |                     |                     |                                      | not matched but controlled and gender is not significantly different, age is higher in cases                            |   |                     | all BSI                | 30 days  |   |   |  |   |
| 16 | Kaya, 2013              | Score      | -  | Mix   | 44 cases<br>69 controls   | -                  | -                   | ++                  | -                                    | ++  | ++  | -                   | -                      | +  | c.b.e   | -   | Mort. cases=36.4%<br>Mort. controls= 27.5%   | no data   |
|    |                         | Comments   | Retrospective case-control study           | Cases: 51.4% hospital onset, 38.6% community onset                  |   |                    |                     |                     |                                      | not matched but controlled in univariate analyses   |   |                     | all BSI                | mortality in hospital                                    |   |   |  |   |
| 17 | Kim, 2013               | Score      | -  | HCA   | 15 cases<br>72 controls   | -                  | +                   | ++                  | -                                    | ++  | c.b.e   | c.b.e               | -                      | ++   | ++  | c.b.e   | Mort. cases=6.7%<br>Mort. controls= 5.5%   | no data   |
|    |                         | Comments   | Retrospective study                        |   | patients who had hematological diseases and neutropenic fever   |                    |                     |                     |                                      | data for EC not available because pooled with KP cases  | data for EC not available because pooled with KP cases  |                     | all BSI                | 30 days  | data for EC not available because pooled with KP cases  | mortality data extracted for EC   |  |   |
| 18 | Lambert, 2011           | Score      | -  | Mix   | a)42 cases<br>218 controls<br>b)58 cases<br>464 controls  | -                  | ++                  | ++                  | +                                    | ++  | c.b.e   | -                   | ++                     | ++   | c.b.e   | -   | a) Mort. cases=50%<br>Mort. controls=40%<br>aHR=1.3, 95%CI(0.8-2.2)<br>b) Mort. cases=47%<br>Mort. controls=29%<br>aHR=1.4, 95%CI(0.9-2.3) | from infection to discharge*<br>median (IQR);<br>a)cases=16(4-24);controls=9(5-20)<br>b)cases=18(11-29);<br>controls=17(9-29) |
|    |                         | Comments   | Retrospective cohort study                 | no specific information available                                   | a)BSI<br>b)pneumonia  | ICU patients       |                     |                     |                                      |   |   |                     | all ICU patients       | mortality in hospital                                    |   | a)BSI<br>b)pneumonia  | for those discharged alive   |   |
| 19 | Leistner, 2014 a        | Score      | -  | Mix   | 115 cases<br>983 controls   | -                  | ++                  | ++                  | ++                                   | ++  | -   | -                   | -                      | +  | c.b.e   | -   | Mort. cases=26%<br>Mort. controls=18%  | median (range)<br>cases=27 (12-53)<br>controls=15 (8-32)  |
|    |                         | Comments   | Retrospective cohort study                 | HCA: 58% cases, 38% controls  |   |                    |                     |                     |                                      |   |   |                     | all BSI                | mortality in hospital                                    |   |   |  |   |
| 20 | Leistner, 2014 b        | Score      | -  | Mix   | 178 cases<br>1322 controls  | -                  | ++                  | ++                  | ++                                   | ++  | c.b.e   | c.b.e               | -                      | +  | c.b.e   | c.b.e   | Mort. cases=25.3%<br>Mort. controls=17.6%  | no specific data  |
|    |                         | Comments   | Retrospective cohort study                 | no specific information available                                   |   |                    |                     |                     |                                      | no information because data are pooled with KP infections   | no information because data are pooled with KP infections   |                     | all BSI                | mortality in hospital                                    | no information because data are pooled with KP infections   |   |  |   |
| 21 | Mantellus, 2016         | Score      | -  | HCA   | 182 cases<br>2035 controls  | -                  | ++                  | ++                  | ++                                   | ++  | ++  | -                   | -                      | +  | ++  | -   | a)Mort. cases=7.7%<br>Mort. controls= 5.9%<br>b)Mort. cases=14.3%<br>Mort. controls=11.9%  | no data   |
|    |                         | Comments   | Retrospective study                        |   |   |                    |                     |                     |                                      | not matched but controlled in univariate analyses   |   |                     | all BSI                | a) 7 days<br>b) 28 days                                  |   | a) 7 days<br>b) 28 days   |  |   |
| 22 | Park, 2011              | Score      | -  | Mix   | 50 cases<br>100 controls  | -                  | +                   | ++                  | ++                                   | ++  | ++  | -                   | -                      | +  | ++  | -   | a)Mort. cases=8%<br>Mort. controls= 6%<br>b)Mort. cases=16%<br>Mort. controls=8%<br>OR=6.4, 95%CI(0.3-145.5)                               | no data   |
|    |                         | Comments   | Retrospective cohort study                 | HCA   | community onset BSI   |                    |                     |                     |                                      | not matched but controlled in univariate analyses   |   |                     | all BSI                | a) 7 days<br>b) 30 days                                  |   | a) 7 days<br>b) 30 days   |  |   |
|    |                         | Score      | -  | HCA   | 11 cases<br>77 controls   | -                  | +                   | ++                  | -                                    | ++  | ++  | -                   | -                      | +  | c.b.e   | ++  | Mort. cases=27.3%<br>Mort. controls= 3.9%  | no data   |
|    |                         | Comments   |  |   |   |                    |                     |                     |                                      | not matched but controlled in univariate analyses   |   |                     | all BSI                |  |   |   |  |   |





| CREC Checklist for the evaluation of the most relevant studies for building antimicrobial resistance (AMR) outcome trees, healthcare-associated infection (HAI) attributable case fatality and attributable length-of-stay (LOS) |                    |            |                                |   |   |                         |                         |                         |  |                         |   |   |                         |                         |  |   |   |  |
|--|--------------------|------------|--------------------------------|---|---|-------------------------|-------------------------|-------------------------|--|-------------------------|---|---|-------------------------|-------------------------|--|---|---|--|
| Nr   | Study              | Study type | Infection type                 | N (cases,controls)  | Sample size   |                         |                         | Representativeness      |  |                         | Matching or controlling for confounders               |   |                         |                         |  | Statistically significant outcome results   | Risk difference   |  |
|  |                    |            |                                |   | calculation a priori  | Geographical            | Demographical           | Clinical                | Exclusion/inclusion criteria   | Demographics            | Underlying disease                                    | Infection site  | Hospital and unit/ward  | Follow-up               | Case fatality                                |   | LOS   |  |
|  | First author, year |            | HCA; CA; Mix; c.b.e            |   | □ ++; □ +; □ -; □ c.b.e   | □ ++; □ +; □ -; □ c.b.e | □ ++; □ +; □ -; □ c.b.e | □ ++; □ +; □ -; □ c.b.e | □ ++; □ +; □ -; □ c.b.e  | □ ++; □ +; □ -; □ c.b.e | □ ++; □ +; □ -; □ c.b.e                               | □ ++; □ +; □ -; □ c.b.e                               | □ ++; □ +; □ -; □ c.b.e | □ ++; □ +; □ -; □ c.b.e | □ ++; □ +; □ -; □ c.b.e                      | %; RR; OR; aHR, etc   | (days)  |  |
| 1  | Chang, 2011        | Score      | ++                             | Mix   | 17 cases<br>34 controls   | -                       | +                       | ++                      | ++   | ++                      | ++  | -   | -                       | +                       | ++   | +++   | a) Mort.cases=47.06%<br>Mort.controls=28.24%<br>b) Mort.cases=70.59%<br>Mort.controls=47.06%<br>c) Mort.cases=94.12%<br>Mort.controls=50% | mean±SD (min-max)<br>cases=58.4 (56.4-71.6)<br>controls=35.8±34.5 (4-141)                      |
|  |                    | Comments   | Matched case-control study     | *mostly HCA* but not specified                                      | Cases are non-susceptible (i.e. resistant and intermediate MIC values) but was not possible to differentiate them |                         |                         |                         |  |                         |   |   |                         | all BSI                 | a) ≤14 days<br>b) ≤ 28 days<br>c) hospitaliz | *only mortality during hospitalization was significantly higher in cases compared to controls | a) ≤14 days<br>b) ≤ 28 days<br>c) hospitaliz  |  |
| 1  | Epstein, 2014      | Score      | +                              | HCA   | 8 cases<br>27 controls  | -                       | +                       | ++                      | +  | ++                      | ++  | -   | -                       | ++                      | c.b.e.                                       | c.b.e.  | Mort.cases=25%<br>Mort.controls=0%  | median cases=8.5<br>mean(SD)(range)<br>cases=13.3 (12.0) [1-37]<br>controls=30.2 (13.2) [4-65] |
|  |                    | Comments   | Prospective case-control study | cases exposed to duodenoscopes, considered the source of infection  |   |                         |                         |                         | cases are exposed to duodenoscopes and controls are from rehabilitation ward |                         |   | not matched but controlled in the univariate analyses |                         |                         | hospitalization                              | no information  | *death not related to CREC  |  |
| 1  | Ahn, 2014          | Score      | ++                             | Mix   | 57 cases<br>114 controls  | -                       | +                       | ++                      | ++   | ++                      | ++  | -   | ++                      | +                       | ++   | -   | Mort.cases=14.8%<br>Mort.controls=10.2%   | mean±SD cases=26.8±37.9<br>controls=13.1±41.3  |
|  |                    | Comments   | Matched case-control study     | HCA: 84.2% cases, 71.9% controls<br>CA: 15.8% cases, 28.1% controls |   |                         |                         |                         |  |                         | not matched but controlled in the univariate analyses |   |                         |                         | 28 days                                      |   |   |  |

**Sample size** N refers to total number of cases and controls (no score)  
**Calculation a priori:** ++ if performed (e.g. based on expected prevalence or on literature data) or the study refers to large national surveys; - if not performed  
**Study type:** ++ matched cohort or case-control studies; + prospective cohort or case-control studies; - retrospective database studies  
**Infection type** HCA: health-care associated; CA: community associated; Mix: health-care and community associated together  
**Representativeness** Geographical: ++ if the study was conducted in an EU/EEA setting; + if the study was conducted in high-income country (ref. World bank); - if the study was not conducted in an EU/EEA or high-income country setting  
Demographical: ++ if the study population represents all age groups; + if the study population represents selected age-specific groups (e.g. elderly, infants); - if the study population represents a selected sex category and age-specific groups  
Clinical: ++ if the study population represents the overall hospital population; + if the study population partially represents the hospital population; - if the study population represents a disease-specific population (e.g. liver transplanted patients, cancer patients, etc.)  
**Exclusion/inclusion criteria:** ++ if the same exclusion/inclusion criteria were adopted for both cases and controls; + if some (but not all) exclusion/inclusion criteria were adopted for both cases and controls; - if exclusion/inclusion criteria were different in cases and controls  
**Demographics:** ++ if performed for age and sex; + if performed only for age or only for sex; - if not performed at all  
**Matching or controlling for confounders** Underlying disease: ++ if performed for two or more criteria (e.g. comorbidity score, McCabe score, severity index, n. comorbidities, allergy, immunosuppression status, prior hospitalization etc.); + if performed for only one criteria; - if not performed at all  
Infection site: ++ if performed; - if not performed  
Hospital and unit/ward: ++ if same hospital and same unit/ward; + if same hospital but different unit/ward; - if not same hospital and/or not same unit/ward  
Follow-up: ++ if ≥ 28 days; - if < 28 days  
**Risk difference** Statistically significant outcome results: ++ if results and 95%CI are statistically significant; - if results and 95%CI are not statistically significant  
Case fatality and LOS refer to risk difference estimates in cases and controls (no score)

|        |  |
|--------|--|
| ++     | Matches completely/fully fulfilled   |
| +      | Matches incompletely but sufficiently/only partly but sufficiently fulfilled |
| -      | Does not match or matches insufficiently/insufficiently fulfilled            |
| c.b.e. | Cannot be evaluated  |

**MBRACI** list for the evaluation of the most relevant studies for building antimicrobial resistance (AMR) outcome trees, healthcare-associated infection (HAI) attributable case fatality and attributable length-of-stay (LOS)

| Study                   | Study type | Infection type      | Sample size        |                      | Representativeness |   |                    | Matching or controlling for confounders |                    |                    |                    |                        |                    | Risk difference                           |                    |        |       |   |  |
|-------------------------|------------|---------------------|--------------------|----------------------|--------------------|---|--------------------|---|--------------------|--------------------|--------------------|------------------------|--------------------|---|--------------------|--------|-------|---|--|
|                         |            |                     | N (cases,controls) | calculation a priori | Geographical       | Demographical   | Clinical           | Exclusion/inclusion criteria            | Demographics       | Underlying disease | Infection site     | Hospital and unit/ward | Follow-up          | Statistically significant outcome results | Case fatality      | LOS    |       |   |  |
| 1st author, year        |            | HCA; CA; Mix; c.b.e |                    | ++; +; -; 0; c.b.e   | ++; +; -; 0; c.b.e | ++; +; -; 0; c.b.e                                      | ++; +; -; 0; c.b.e | ++; +; -; 0; c.b.e                      | ++; +; -; 0; c.b.e | ++; +; -; 0; c.b.e | ++; +; -; 0; c.b.e | ++; +; -; 0; c.b.e     | ++; +; -; 0; c.b.e | ++; +; -; 0; c.b.e                        | % RR; OR; aHR; etc | (days) |       |   |  |
| BSI R vs NI             | 1          | Al Jarousha, 2009   | Score              | +                    | HCA                | 40 cases<br>100 controls                                | -                  | -                                       | +                  | -                  | ++                 | ++                     | -                  | -   | -                  | c.b.e  | ++    | Mort. cases=37.5%<br>Mort. controls=12%   | no specific data   |
|                         | 2          | Gulen, 2015         | Score              | -                    | HCA                | 41 cases<br>45 controls*                                | -                  | -                                       | ++                 | +                  | ++                 | ++                     | -                  | -   | ++                 | ++     | c.b.e | a) Mort. cases=30%<br>b) Mort. cases=52.4%<br>c) Mort. cases=53.7%<br>Attrib. mort.=24.4%                                 | before BSI<br>mean±SD<br>cases=25.49±21.47<br>controls=22.80±19.28                           |
| BSI R vs S              | 1          | Anunnatsiri, 2011   | Score              | -                    | Mix                | 24 cases<br>25 controls                                 | -                  | -                                       | ++                 | ++                 | ++                 | ++                     | -                  | -   | +                  | c.b.e  | ++    | Mort. cases=91.7%<br>Mort. controls=48%<br>OR=11.92; 95%CI(2.30-61.83)  | before BSI<br>median (range)<br>cases=21.5(4-161)<br>controls=14(2-86)                       |
|                         | 2          | Fitzpatrick, 2015   | Score              | -                    | Mix                | 92 cases<br>24 controls                                 | -                  | +                                       | ++                 | ++                 | ++                 | ++                     | -                  | -   | +                  | ++     | ++    | a) Mort. cases=36%<br>Mort. controls=8%<br>b) Mort. cases=44%<br>Mort. controls=8%  | postculture<br>median(range)<br>cases=11.5(2-69)<br>controls=6(2-38)                         |
|                         | 3          | Guo, 2016           | Score              | -                    | c.b.e              | 54 cases<br>23 controls                                 | -                  | -                                       | ++                 | ++                 | ++                 | -                      | -                  | +   | ++                 | ++     | ++    | Mort. cases=44.8%<br>Mort. controls=4.3%<br>OR=26.3; 95%CI(3.0-231.4)   | in ICU<br>mean<br>cases=51<br>controls=5   |
|                         | 4          | Lee, 2007           | Score              | ++                   | HCA                | 46 cases<br>46 controls                                 | -                  | +                                       | ++                 | ++                 | ++                 | ++                     | -                  | -   | +                  | c.b.e  | ++    | a) Mort. cases=47.8%<br>Mort. controls=39.1%<br>b) Mort. cases=34.8%<br>Mort. controls=13.0%                              | mean±SD<br>cases=54.2±42.8<br>controls=34.1±30.5   |
|                         | 5          | Lee, 2010           | Score              | -                    | Mix                | 147 cases<br>144 controls                               | -                  | +                                       | ++                 | ++                 | ++                 | c.b.e                  | c.b.e              | -   | +                  | ++     | ++    | Mort. cases=32%<br>Mort. controls=8.3%<br>OR=7.46; 95%CI(3.78-14.70)  | no specific data   |
|                         | 6          | Smolyako, 2003      | Score              | +                    | HCA                | 51 cases<br>43 controls                                 | -                  | +                                       | ++                 | ++                 | ++                 | +                      | -                  | -   | +                  | c.b.e  | ++    | Mort. cases=29.4%<br>Mort. controls=11.6%<br>OR=4   | mean±SD<br>cases=37.7±30<br>controls=24.3±18.3   |
| Resp. Tract R vs S      | 1          | Cai, 2012           | Score              | +                    | HCA                | 116 cases<br>45 controls                                | -                  | -                                       | +                  | +                  | ++                 | +                      | +                  | -   | +                  | c.b.e  | ++    | Mort. cases=18.26%<br>Mort. controls=4.44%  | in ICU<br>mean±SD<br>cases=17.39±7.05<br>controls=14.43±3.92                                 |
|                         | 2          | Inchai, 2015        | Score              | -                    | HCA                | 72 cases<br>33 controls                                 | -                  | -                                       | ++                 | +                  | ++                 | ++                     | -                  | -   | +                  | ++     | -     | a) Mort. cases=31.9%<br>Mort. controls=21.2%<br>b) Mort. cases=44.4%<br>Mort. controls=27.3%<br>HR=1.03; 95%CI(0.44-2.45) | no data  |
|                         | 3          | Park, 2006          | Score              | -                    | HCA                | 17 cases<br>30 controls                                 | c.b.e              | +                                       | c.b.e              | -                  | c.b.e              | -                      | ++                 | -   | +                  | c.b.e  | -     | Mort. cases=58.8%<br>Mort. controls=40%   | mean±SD<br>cases=42.8±24.0<br>controls=66.2±56.1   |
| Mixed inf. site R vs NI | 1          | Abbo, 2007          | Score              | ++                   | c.b.e              | 118 cases<br>118 controls                               | -                  | +                                       | ++                 | ++                 | ++                 | ++                     | -                  | -   | +                  | c.b.e  | ++    | Mort. cases=36%<br>Mort. controls=11%<br>OR=2.21; 95%CI(1.17-4.16)  | median<br>cases=17<br>controls=11  |
|                         | 2          | Fukuta, 2013        | Score              | -                    | c.b.e              | 31 cases<br>62 controls                                 | -                  | +                                       | ++                 | +                  | ++                 | ++                     | +                  | -   | +                  | ++     | -     | Mort. cases=41.9%<br>Mort. controls=29%   | median(QR)<br>cases=28 (9-59)<br>controls=10(5-18)   |
|                         | 3          | Lee, 2016           | Score              | ++                   | HCA                | 122 cases<br>122 controls                               | -                  | +                                       | ++                 | +                  | ++                 | ++                     | ++                 | -   | ++                 | c.b.e  | ++    | Mort. cases=49.2%<br>Mort. controls=32%<br>OR=3.64; 95%CI(1.80-7.37)  | mean±SD<br>cases=40.3±40.6<br>controls=24.6±28   |
|                         | 4          | Brahmi, 2007        | Score              | +                    | HCA                | 29 cases<br>34 controls                                 | -                  | -                                       | ++                 | +                  | ++                 | +                      | ++                 | -   | ++                 | c.b.e  | ++    | Mort. cases=67.5%<br>Mort. controls=46.7%   | in ICU<br>mean±SD<br>cases=27±17.8<br>controls=32.3±23.9                                     |
|                         | 5          | Daniels, 2008       | Score              | -                    | HCA                | 4146 cases<br>42 controls<br>b) 42 cases<br>42 controls | -                  | +                                       | ++                 | ++                 | ++                 | ++                     | ++                 | ++  | ++                 | ++     | ++    | -   | a) Mort. cases=15.6%<br>Mort. controls=9.5%<br>b) Mort. cases=14.3%<br>Mort. controls=5.5%   |
| Mixed inf. site R vs S  | 1          | Lemos, 2011         | Score              | +                    | HCA                | 103 cases<br>62 controls                                | -                  | -                                       | ++                 | +                  | ++                 | ++                     | -                  | -   | -                  | ++     | ++    | a) Mort. cases=31%<br>Mort. controls=9%<br>b) Mort. cases=41%<br>Mort. controls=9%<br>b) RR=1.219;<br>95%CI(0.923-1.611)  | median(QR)<br>pre ICU<br>cases=(11.5-22.3)<br>in ICU<br>cases=15(13-60)<br>controls=13(8-44) |
|                         | 2          | Pierri, 2015        | Score              | ++                   | HCA                | 14 cases<br>26 controls                                 | -                  | ++                                      | ++                 | +                  | ++                 | ++                     | ++                 | -   | ++                 | c.b.e  | -     | Mort. cases=57%<br>Mort. controls=46%   | mean±SD<br>cases=36±20<br>controls=25±18   |
|                         | 3          | Zilberberg, 2016    | Score              | -                    | Mix                | 1171 cases<br>252 controls                              | -                  | +                                       | ++                 | ++                 | ++                 | +                      | -                  | ++  | -                  | c.b.e  | ++    | Mort. cases=23.7%<br>Mort. controls=12.7%   | no data  |

Sample size: N refers to total number of cases and controls (no score)  
**Calculation a priori:** ++ if performed (e.g. based on expected prevalence or on literature data) or the study refers to large national surveys; - if not performed  
**Study type:** ++ matched cohort or case-control studies; + prospective cohort or case-control studies; - retrospective database studies  
**Infection type:** HCA: health-care associated; CA: community associated; Mix: health-care and community associated together  
**Geographical:** ++ if the study was conducted in an EU/EEA setting; + if the study was conducted in high-income country (ref. World Bank); - if the study was not conducted in an EU/EEA or high-income country setting  
**Demographical:** ++ if the study population represents all age groups; + if the study population represents selected age-specific groups (e.g. elderly, infants); - if the study population represents a selected sex category and age-specific groups  
**Clinical:** ++ if the study population represents the overall hospital population; + if the study population partially represents the hospital population; - if the study population represents a disease-specific population (e.g. liver transplanted patients, cancer patients, etc.)  
**Exclusion/inclusion criteria:** ++ if the same exclusion/inclusion criteria were adopted for both cases and controls; + if some (but not all) exclusion/inclusion criteria were adopted for both cases and controls; - if exclusion/inclusion criteria were different in cases and controls  
**Demographics:** ++ if performed for age and sex; + if performed only for age or only for sex; - if not performed at all  
**Matching or controlling for underlying disease:** ++ if performed for two or more criteria (e.g. comorbidity score, McCabe score, severity index, n. comorbidities, allergy, immunosuppression status, prior hospitalisation, etc.); + if performed for only one criteria; - if not performed at all  
**Infection site:** ++ if performed; - if not performed  
**Hospital and unit/ward:** ++ if same hospital and same unit/ward; - if not same hospital and/or not same unit/ward  
**Follow-up:** ++ if ≥ 28 days; - if < 28 days  
**Statistically significant outcome results:** ++ if results and 95%CI are statistically significant; - if results and 95%CI are not statistically significant  
**Case fatality and LOS:** refer to risk difference estimates in cases and controls (no score)

|        |  |
|--------|--|
| ++     | Matches completely/fully fulfilled   |
| +      | Matches incompletely but sufficiently/only partly but sufficiently fulfilled |
| -      | Does not match or matches insufficiently/insufficiently fulfilled            |
| c.b.e. | Cannot be evaluated  |

CRACI

Checklist for the evaluation of the most relevant studies for building antimicrobial resistance (AMR) outcome trees, healthcare-associated infection (HAI) attributable case fatality and attributable length-of-stay (LOS)

| Nr                      | Study              | Study type                                    | Infection type      | Sample size  |  | Representativeness  |  |  | Matching or controlling for confounders                       |   |  |  |  | Statistically significant outcome results  | Risk difference                               |                 |   |  |   |
|-------------------------|--------------------|---|---------------------|--|--|---|--|--|---|---|--|--|--|--|---|-----------------|---|--|---|
|                         |                    |   |                     | N (cases/controls)   | calculation a priori   | Geographical  | Demographical  | Clinical   | Exclusion/inclusion criteria                                  | Demographics  | Underlying disease   | Infection site                                   | Hospital and unit/ward   |  | Follow-up                                     | Case fatality   | LOS   |  |   |
|                         | First author, year |   | HCA; CA; Mix; c.b.e |  | 0 ++; 0-0 c.b.e  | 0 ++; 0-0 c.b.e   | 0 ++; 0-0 c.b.e  | 0 ++; 0-0 c.b.e  | 0 ++; 0-0 c.b.e   | 0 ++; 0-0 c.b.e                                       | 0 ++; 0-0 c.b.e  | 0 ++; 0-0 c.b.e                                  | 0 ++; 0-0 c.b.e  | 0 ++; 0-0 c.b.e  | 0 ++; 0-0 c.b.e                               | 0 ++; 0-0 c.b.e | 0 ++; 0-0 c.b.e   |  |   |
| BSI R vs NI             | 1                  | Kim, 2014                                     | Score               | -  | HCA  | 19 cases<br>38 controls   | -  | +  | ++  | -   | ++   | ++   | +  | -  | ++  | c.b.e           | ++  | Mort. rate cases=94.7%<br>Mort. rate controls=8.3%   | median (range)<br>cases=35(30-47)<br>controls=29(26.75-34)        |
|                         |                    |   | Comments            | Retrospective case-control study                                   | not explicitly said in the article, but very specific patients |   |  |  | hemopoietic stem-cell transplantation recipients              | hemopoietic stem-cell transplantation recipients      | not matched but differences were not significant           | hemopoietic stem-cell transplantation recipients | all BSI  | mortality in hospital  | Fisher's exact test on the fatality rates     |                 |   |  |   |
| BSI R vs S              | 2                  | Thairimontichai, 2013                         | Score               | -  | HCA  | 14 resistant<br>38 sensitive<br>44 controls                             | -  | -  | +   | +   | ++   | -  | +  | -  | ++  | -               | ++  | Mort. rate resist=42.9%<br>Mort. rate sens=13.2%<br>Mort. rate controls=6.8%<br>OR RvsS=5; 95%CI(1.2-20.4)<br>OR RvsNI=10.2; 95%CI(2.1-50)   | median (range)<br>cases=161(1-300)<br>controls=24.5(1-108)        |
|                         |                    |   | Comments            | Case-control study   | not explicitly said in the article, but very specific patients |   |  | neonates   | neonates in ICU   | not matched but all were neonates                     | presence in ICU  | all BSI  | all in NICU  | 7 days mortality   | OR for mortality                              |                 |   |  |   |
| BSI R vs S              | 1                  | Deris, 2011                                   | Score               | -  | HCA  | 15 cases<br>41 controls   | -  | -  | ++  | ++  | ++   | ++   | -  | -  | +   | c.b.e           | -   | Mort. rate cases=64.3%<br>Mort. rate controls=40.5%<br>OR (95%CI)=0.38 (0.11-1.36)<br>*Attrib. mort. rate cases=42.9%<br>Attrib. mort. rate controls=24.3%<br>OR (95%CI)=2.33(0.64-8.65) | median (IQR)<br>cases=32.3(16.4-48.8)<br>controls=32.8(25.0-40.6) |
|                         |                    |   | Comments            | Cross sectional case-control study                                 |  |   |  |  |   | not matched but differences were not significant      |  | all BSI  | mortality in hospital  | neither the all-cause nor the attributable mortality   | * within 72h from isolation                   |                 |   |  |   |
| BSI R vs S              | 2                  | Esterly, 2011                                 | Score               | -  | c.b.e  | 37 cases<br>42 controls   | -  | +  | ++  | ++  | ++   | +  | -  | +  | c.b.e   | a) ++<br>b) -   | Mort. rate cases=56.8%<br>Mort. rate controls=23.8%<br>Mort. rate resist=13.2%<br>Mort. rate sens=13.2%<br>OR=0.58; 95%CI(0.037-9.22)   | Prior isolation<br>median (IQR)<br>cases=161(1-300)<br>controls=24.5(1-108)  |   |
|                         |                    |   | Comments            | Retrospective cohort study   | no information available in the article                        |   |  |  |   | not matched but controlled in the multivariate models | multivariate analysis controlled for underlying conditions | all BSI  | mortality in hospital  | a) comparison of mortality rates<br>b) OR multivariate analyses (none significant)             |   |                 |   |  |   |
| BSI R vs S              | 3                  | Huang, 2012                                   | Score               | -  | c.b.e  | 62 cases<br>164 controls  | -  | +  | ++  | ++  | ++   | ++   | -  | +  | -   | ++              | Mort. rate cases=35.5%<br>Mort. rate controls=20.7%<br>OR=1.03; 95%CI(0.48-2.20)  | Prior isolation<br>mean±SD<br>cases=35.9±33.6<br>controls=28.2±44  |   |
|                         |                    |   | Comments            | Retrospective cohort study   | no information available in the article                        |   |  |  |   | not matched but differences were not significant      | not matched, but controlled for Apache II score            | all BSI  | 14 days  | Resistance was significant for mortality in a univariate analyses, but not in the multivariate |   |                 |   |  |   |
| BSI R vs S              | 4                  | Jumalitrat, 2009                              | Score               | -  | HCA  | 67 cases<br>131 controls  | -  | -  | ++  | ++  | ++   | ++   | -  | +  | -   | ++              | Mort. rate cases=52.2%<br>Mort. rate controls=19.9%<br>aHR=1.7; 95%CI(0.9-2.9)  | median a(IQR)<br>cases=37±32<br>controls=27±37   |   |
|                         |                    |   | Comments            | Retrospective cohort study   |  |   |  |  | >15 years   | not matched but controlled in the HR model            | controlled for ASA score in aHR                            | all BSI  | mortality in hospital  | significant only the difference between the mortality rates                                    |   |                 |   |  |   |
| BSI R vs S              | 5                  | Kim 2012                                      | Score               | -  | c.b.e  | 53 cases<br>42 controls   | -  | +  | ++  | ++  | ++   | ++   | -  | +  | -   | ++              | Mort. rate cases=49.1%<br>Mort. rate controls=9.5%<br>OR=7.29; 95%CI(1.57-33.8)   | Prior isolation<br>mean±SD<br>cases=30.0±33.3<br>controls=30.4±68.3  |   |
|                         |                    |   | Comments            | Retrospective study  | no information available in the article                        |   |  | >16 years  | not matched but controlled in the univariate analyses         |   | all BSI  | 14 days  | significant OR   |  |   |                 |   |  |   |
| BSI R vs S              | 6                  | Kumar 2014                                    | Score               | -  | HCA  | 33 cases<br>32 controls   | -  | -  | +   | +   | ++   | -  | -  | ++   | c.b.e   | -               | Mort. rate cases=27.3%<br>Mort. rate controls=9.4%  | no data  |   |
|                         |                    |   | Comments            | Retrospective chart review   |  |   | neonates   | neonates in ICU  |   | neonates in ICU                                       | all BSI  | all in NICU                                      | mortality in hospital  |  |   |                 |   |  |   |
| BSI R vs S              | 7                  | Routsis, 2010                                 | Score               | +  | HCA  | 30 cases<br>66 controls   | -  | ++   | ++  | +   | ++   | ++   | -  | ++   | c.b.e   | -               | Mort. rate cases=43.3%<br>Mort. rate controls=46.9%   | median (IQR)<br>cases=33(18.8-55.8)<br>controls=28.8(14.5-51.0)  |   |
|                         |                    |   | Comments            | Prospective observational study                                    | not explicitly said in the article, but very specific patients |   |  | only ICU patients  | not matched but controlled in the univariate analyses         |   | all BSI  | all in ICU                                       | mortality in hospital  |  |   |                 |   |  |   |
| BSI R vs S              | 8                  | Tal-Jasper 2016                               | Score               | -  | c.b.e  | 149 cases<br>91 controls  | -  | +  | ++  | ++  | ++   | +  | -  | +  | ++  | ++              | a) Mort. rate cases=70.5%<br>Mort. rate controls=45.1%<br>b) Mort. rate cases=45.1%<br>Mort. rate controls=44.4%<br>Mort. rate resist=73.6%<br>Mort. rate sens=53.3%<br>OR 90days=0.6; 95%CI(0.1-2.3) | median (IQR)<br>cases=21(10.8-39.5)<br>controls=10(7-20.5)   |   |
|                         |                    |   | Comments            | Retrospective cohort study   | no information available in the article                        |   |  |  | not matched but controlled in the univariate analyses for age |   | all BSI  | a) in hospital<br>b) 30 days<br>c) 90 days       | differences between mortality rates were always significant, OR was significant only for 90 days |  |   |                 |   |  |   |
| Resp. Tract R vs NI     | 1                  | Thairimontichai, 2016                         | Score               | -  | HCA  | 63 resistant<br>13 sensitive<br>25 non-infected                         | -  | -  | +   | +   | ++   | ++   | +  | -  | ++  | c.b.e           | ++  | Mort. rate resist=15.9%<br>Mort. sens=7.7%<br>Mort. NI=0%  | median (range)<br>resist=29(8-93)<br>sens=20(8-31)<br>NI=22(8-68) |
|                         |                    |   | Comments            | Retrospective case-control study                                   | not explicitly said in the article, but very specific patients | resistants include also intermediate MIC values (numbers not specified) | all neonates   | all neonates in ICU with VAP                               | not matched but controlled in the univariate analyses         | VAP   | all resp. Tract infections                                 | all in NICU                                      | mortality in hospital  | significant difference between the mortality rates of R vs NI                                  |   |                 |   |  |   |
| Resp. Tract R vs S      | 1                  | Chang, 2011                                   | Score               | -  | HCA  | 93 cases<br>87 controls   | -  | +  | ++  | ++  | ++   | ++   | -  | +  | c.b.e   | ++              | Mort. rate cases=61.3%<br>Mort. rate controls=46.0%   | after VAP onset<br>median±SD<br>cases=23.1±24.3<br>controls=26.7±24.3  |   |
|                         |                    |   | Comments            | Retrospective observational study                                  |  |   |  |  | not matched but controlled in the univariate analyses         |   | all resp. Tract infections                                 | mortality in hospital                            | comparison of mortality rates  |  |   |                 |   |  |   |
| Resp. Tract R vs S      | 2                  | Garnacho-Montero, 2003                        | Score               | +  | HCA  | 21 cases<br>14 controls   | -  | ++   | ++  | +   | ++   | ++   | -  | ++   | c.b.e   | -               | Mort. rate cases=61.9%<br>Mort. rate controls=64.2%<br>*VAP related mortality<br>Mort. rate cases=38%<br>Mort. rate controls=35.7%  | mean±SD<br>cases=45.2±30.7<br>controls=53.9±50   |   |
|                         |                    |   | Comments            | Prospective cohort study   | not explicitly said in the article, but very specific patients |   | ICU patients   | not matched but controlled for Apache II and SOFA          |   | all resp. Tract infections                            | all in ICU   | mortality in hospital                            | no difference in any mortality   | * occurred during the treatment period, when the signs of pneumonia remained, an               |   |                 |   |  |   |
| Resp. Tract R vs S      | 3                  | Zheng, 2013                                   | Score               | -  | HCA  | 97 cases<br>145 controls  | -  | -  | ++  | ++  | ++   | ++   | -  | +  | ++  | ++              | Mort. rate cases=45.6%<br>Mort. rate controls=29.9%   | before pneum<br>mean±SD<br>cases=17.7±6.6<br>controls=18±6.2   |   |
|                         |                    |   | Comments            | Retrospective study  |  |   |  | not matched but controlled in the univariate analyses      |   | all resp. Tract infections                            |  | comparison of mortality rates                    |  |  |   |                 |   |  |   |
| Mixed inf. site R vs NI | 1                  | Henig, 2015                                   | Score               | ++   | Mix  | 1190 cases<br>1190 controls   | -  | +  | ++  | ++  | ++   | +  | ++   | -  | ++  | c.b.e           | ++  | Mort. rate cases=73%<br>Mort. rate controls=55%<br>aHR=2.33; 95%CI(2.08-2.6)   | median (range)<br>cases=18 (0-97)<br>controls=17 (0-96)           |
|                         |                    |   | Comments            | Matched case-control study   | no information on the proportion HCA/CA                        |   |  |  | matched for age   | Charlson index is a matching criteria                 |  | not defined, most probably hospitalization       | significant aHR, no info on the comparison of mortality rates                                    |  |   |                 |   |  |   |
| Mixed inf. site R vs NI | 2                  | Nazer, 2015                                   | Score               | ++   | HCA  | 142 cases<br>232 controls   | -  | -  | ++  | -   | ++   | ++   | ++   | -  | ++  | c.b.e           | ++  | Mort. rate cases=73%<br>Mort. rate controls=61.2%  | median (IQR)<br>cases=12(6-13)<br>controls=3(1-7)                 |
|                         |                    |   | Comments            | Matched case-control study   | not explicitly said in the article, but very specific patients |   | critically ill patients with cancer in ICU                     |  |   |   |  | all in ICU                                       | mortality in ICU   | comparison of mortality rates  |   |                 |   |  |   |
| Mixed inf. site R vs S  | 1                  | Aydemir, 2012                                 | Score               | -  | HCA  | 110 cases<br>55 controls  | -  | -  | ++  | ++  | ++   | ++   | -  | +  | c.b.e   | -               | Mort. rate cases=61.8%<br>Mort. rate controls=52.7%   | after isolation<br>mean±SD<br>cases=18.1±14.0<br>controls=15.7±12.3  |   |
|                         |                    |   | Comments            | Retrospective case-control study                                   |  |   | >16 years  | not matched but controlled in the univariate analyses      |   |   |  | mortality in ICU                                 |  |  |   |                 |   |  |   |
| Mixed inf. site R vs S  | 2                  | de Gouvea, 2012                               | Score               | -  | HCA  | 18 cases<br>31 controls   | -  | -  | ++  | -   | +  | ++   | -  | +  | ++  | -               | Mort. rate cases=44.4%<br>Mort. rate controls=29.0%<br>Inf. related, OR=0.73;<br>95%CI(0.12 - 4.47)<br>Overall mort. OR=1.93;<br>95%CI(0.48 - 7.85)   | no data  |   |
|                         |                    |   | Comments            | Retrospective study  |  | liver and kidney transplant patient                                     | not matched but controlled in the univariate analyses          |  |   |   |  | 30 days  | none of the data on mortality is significant   |  |   |                 |   |  |   |
| Mixed inf. site R vs S  | 3                  | del Mar, 2005                                 | Score               | c.b.e  | HCA  | 30 cases<br>31 controls   | -  | ++   | ++  | +   | ++   | ++   | -  | ++   | c.b.e   | -               | Mort. rate cases=43.3%<br>Mort. rate controls=19%<br>*Related mortality=30%   | attributable LOS=14 days   |   |
|                         |                    |   | Comments            | Case-control study (Not specified if prospective or retrospective) | it was an hospital outbreak                                    | RU and ICU patients   | not matched but controlled in the univariate analyses          |  |   |   |  | RU and ICU                                       | 30 days  | * when infection was established, by clinical criteria, as the primary cause of death          |   |                 |   |  |   |
| Mixed inf. site R vs S  | 4                  | Lautenbach, 2009                              | Score               | +  | c.b.e  | 89 cases<br>297 controls  | -  | +  | ++  | ++  | ++   | -  | -  | -  | ++  | -               | Mort. rate cases=18%<br>Mort. rate controls=21.2%<br>RR=0.85; 95%CI(0.52-1.39)  | median (range)<br>cases=18(12-18)<br>controls=16(12-18)  |   |
|                         |                    |   | Comments            | Prospective cohort study   | no information available in the article                        | significant difference in age   |  |  |   |   |  | 2 hospitals                                      | 30 days  |  |   |                 |   |  |   |
| Mixed inf. site R vs S  | 5                  | Lemos, 2014 a                                 | Score               | +  | c.b.e  | 104 cases<br>61 controls  | -  | -  | ++  | +   | ++   | +  | -  | ++   | ++  | -               | Mort. rate cases=40%<br>Mort. rate controls=12.2%<br>aHR=1.45; 95%CI(0.74-2.87)   | adjusted mean(range)<br>cases=19.3(16-22.5)<br>controls=16.2(11.5-19.9)  |   |
|                         |                    |   | Comments            | Prospective, multicentre cohort study                              | no information available in the article                        |   | ICU patients   | not matched but controlled, age is significantly different |   |   |  | 30 days  |  |  |   |                 |   |  |   |
| Mixed inf. site R vs S  | 6                  | Lemos, 2014 b                                 | Score               | -  | NA   | 1013 cases<br>1553 controls   | -  | c.b.e  | ++  | ++  | c.b.e  | -  | -  | -  | c.b.e   | ++              | crude OR=2.22<br>95% CI=1.66-2.98   |  |   |
|                         |                    |   | Comments            | Systematic review and meta-analysis                                | sum of cases and controls of all studies                       | studies from all the world  | the criteria refer to the included studies                     |  |   |   |  | study specific                                   |  |  |   |                 |   |  |   |
| Mixed inf. site R vs S  | 7                  | Sheng, 2010                                   | Score               | -  | HCA  | a)30 cases<br>30 controls<br>b) 91 cases<br>97 controls                 | -  | +  | ++  | ++  | ++   | ++   | ++   | -  | ++  | ++              | a)Mort. rate cases=13.3%<br>Mort. rate controls=20%<br>b)Mort. rate cases=33%<br>Mort. rate controls=17.5%  | after isolation<br>median (range)<br>a)cases=41 (5-292)<br>b) cases=37 (1-216)<br>controls=23 (1-151)  |   |
|                         |                    |   | Comments            | Multicentre retrospective study                                    | a) colonized patients<br>b) infected patients                  | not matched but no significant difference in test distribution          | not matched but no significant difference in test distribution | not matched but controlled in the univariate analyses      |   |   |  | 30 days  | significant only for infection (b)   | a) colonized patients<br>b) infected patients  | a) colonized patients<br>b) infected patients |                 |   |  |   |
| Mixed inf. site R vs S  | 8                  | The Brooklyn Antibiotic Resistance Task Force | Score               | ++   | Mix  | a)44 cases<br>33 controls<br>b) 10 cases<br>10 controls                 | -  | +  | ++  | ++  | ++   | +  | ++   | ++   | c.b.e   | -               | a)Mort. rate cases=34%<br>Mort. rate controls=27%<br>b)Mort. rate cases=20%<br>Mort. rate controls=30%  | after isolation<br>median<br>cases=31.5<br>controls=13   |   |
|                         |                    |   | Comments            |  |  |   |  |  |   |   |  |  |  |  |   |                 |   |  |   |

| Comments | Matched case-control study | 100% of cases and 85% of controls were HCA | a) all cases and control b) matched pairs |  |  |  |  |  |  | matched for age the 10 pairs | only the 10 matched pairs | only the 10 matched pairs | mortality in hospital | none of the data on mortality is significant |  | data not available for group a) |
|----------|----------------------------|--|---|--|--|--|--|--|--|------------------------------|---------------------------|---------------------------|-----------------------|--|--|---------------------------------|
|----------|----------------------------|--|---|--|--|--|--|--|--|------------------------------|---------------------------|---------------------------|-----------------------|--|--|---------------------------------|

**Sample size** N refers to total number of cases and controls (**no score**)  
**Calculation a priori:** ++ if performed (e.g. based on expected prevalence or on literature data) or the study refers to large national surveys; - if not performed

**Study type** HCA: health-care associated; CA: community associated; MC: health-care and community associated together  
**Infection type** **Geographical:** ++ if the study was conducted in an EU/EEA setting; + if the study was conducted in high-income country (ref. World Bank); - if the study was not conducted in an EU/EEA or high-income country setting  
**Representativeness** **Demographical:** ++ if the study population represents all age groups; + if the study population represents selected age-specific groups (e.g. elderly, infants); - if the study population represents a selected sex category and age-specific groups  
**Clinical:** ++ if the study population represents the overall hospital population; + if the study population partially represents the hospital population; - if the study population represents a disease-specific population (e.g. liver transplanted patients, cancer patients, etc.)  
**Exclusion/inclusion criteria:** ++ if the same exclusion/inclusion criteria were adopted for both cases and controls; + if some (but not all) exclusion/inclusion criteria were adopted for both cases and controls; - if exclusion/inclusion criteria were different in cases and controls  
**Demographics:** ++ if performed for age and sex; + if performed only for age or only for sex; - if not performed at all  
**Matching or controlling for confounders** **Underlying disease:** ++ if performed for two or more criteria (e.g. comorbidity score, McCabe score, severity index, n. comorbidities, allergy, immunosuppression status, prior hospitalisation etc.); + if performed for only one criteria; - if not performed at all  
**Infection site:** ++ if performed; - if not performed  
**Hospital and unit/ward:** ++ if same hospital and same unit/ward; + if same hospital but different unit/ward; - if not same hospital and/or not same unit/ward  
**Follow-up:** ++ if ≥ 28 days; - if < 28 days  
**Risk difference** **Statistically significant outcome results:** ++ if results and 95%CI are statistically significant; - if results and 95%CI are not statistically significant  
**Case fatality and LOS** refer to risk difference estimates in cases and controls (**no score**)

Scoring table

|        |   |
|--------|---|
| ++     | Matches completely/is completely fulfilled                                      |
| +      | Matches incompletely but sufficiently/is only partly but sufficiently fulfilled |
| -      | Does not match or matches insufficiently/sufficiently fulfilled                 |
| c.b.e. | Cannot be evaluated   |

| CoRACI Checklist for the evaluation of the most relevant studies for building antimicrobial resistance (AMR) outcome trees, healthcare-associated infection (HAI) attributable case fatality and attributable length-of-stay (LOS) |              |                    |                          |   |  |                      |                    |                    |                    |   |   |                    |                    |                        |                          |   |  |  |
|--|--------------|--------------------|--------------------------|---|--|----------------------|--------------------|--------------------|--------------------|---|---|--------------------|--------------------|------------------------|--------------------------|---|--|--|
| Nr   | Study        | First author, year | Study type               | Infection type                          | Sample size  |                      | Representativeness |                    |                    | Matching or controlling for confounders     |   |                    |                    |                        | Risk difference          |   |  |  |
|  |              |                    |                          |   | N (cases,controls)   | calculation a priori | Geographical       | Demographical      | Clinical           | Exclusion/inclusion criteria                | Demographics  | Underlying disease | Infection site     | Hospital and unit/ward | Follow-up                | Statistically significant outcome results | Case fatality  | LOS  |
|  |              |                    |                          | HCA; CA; Mx; c.b.e                      |  | □ ++; □ +; □ c.b.e   | □ ++; □ +; □ c.b.e | □ ++; □ +; □ c.b.e | □ ++; □ +; □ c.b.e | □ ++; □ +; □ c.b.e                          | □ ++; □ +; □ c.b.e                                    | □ ++; □ +; □ c.b.e | □ ++; □ +; □ c.b.e | □ ++; □ +; □ c.b.e     | □ ++; □ +; □ c.b.e       | □ ++; □ +; □ c.b.e                        | □ ++; □ +; □ c.b.e   |  |
| 1  | Wang, 2015   | Score              | -                        | c.b.e                                   | 58 cases<br>213 controls   | -                    | +                  | ++                 | ++                 | ++  | ++  | -                  | -                  | +                      | -                        | -   | a) Mort. rate cases=10.3%<br>Mort. rate controls=10.3%<br>b) Mort. rate cases=15.5%<br>Mort. rate controls=15% | prior infection median (IQR) cases=56 (32-101) controls=37 (22-65) |
|  |              | Comments           | Retrospective study      | no information available in the article | all patient had A.nosocomialis BSI but all they had also experienced at least one A. baumannii |                      |                    |                    |                    |   | not matched but controlled in the univariate analyses |                    |                    | all BSI infections     | a) 14 days<br>b) 18 days | none of the follow up mortalities         |  |  |
| 1  | Taneja, 2011 | Score              | -                        | c.b.e                                   | 8 cases<br>42 controls   | -                    | -                  | ++                 | -                  | ++  | -   | -                  | -                  | -                      | c.b.e                    | -   | Mort. Rate both groups=0%  | no data  |
|  |              | Comments           | Prospective cohort study | no information available in the article |  |                      |                    |                    |                    | all patients had complicated UTI infections |   |                    |                    | all UTI infections     |                          |   |  |  |

**Sample size** N refers to total number of cases and controls (no score)  
**Calculation a priori**: ++ if performed (e.g. based on expected prevalence or on literature data) or the study refers to large national surveys; - if not performed  
**Study type**: ++ matched cohort or case-control studies; + prospective cohort or case-control studies; - retrospective database studies  
**Infection type** HCA: health-care associated; CA: community associated; Mx: health-care and community associated together  
**Representativeness** **Geographical**: ++ if the study was conducted in an EU/EEA setting; + if the study was conducted in high-income country (ref. World bank); - if the study was not conducted in an EU/EEA or high-income country setting  
**Demographical**: ++ if the study population represents all age groups; + if the study population represents selected age-specific groups (e.g. elderly, infants); - if the study population represents a selected sex category and age-specific groups  
**Clinical**: ++ if the study population represents the overall hospital population; + if the study population partially represents the hospital population; - if the study population represents a disease-specific population (e.g. liver transplanted patients, cancer patients, etc.)  
**Exclusion/inclusion criteria**: ++ if the same exclusion/inclusion criteria were adopted for both cases and controls; + if some (but not all) exclusion/inclusion criteria were adopted for both cases and controls; - if exclusion/inclusion criteria were different in cases and controls  
**Demographics**: ++ if performed for age and sex; + if performed only for age or only for sex; - if not performed at all  
**Matching or controlling for confounders** **Underlying disease**: ++ if performed for two or more criteria (e.g. comorbidity score, McCabe score, severity index, n. comorbidities, allergy, immunosuppression status, prior hospitalisation etc.); + if performed for only one criteria; - if not performed at all  
**Infectious site**: ++ if performed; - if not performed  
**Hospital and unit/ward**: ++ if same hospital and same unit/ward; + if same hospital but different unit/ward; - if not same hospital and/or not same unit/ward  
**Follow-up**: ++ if ≥ 28 days; - if < 28 days  
**Risk difference** **Statistically significant outcome results**: ++ if results and 95%CI are statistically significant; - if results and 95%CI are not statistically significant  
**Case fatality and LOS** refer to risk difference estimates in cases and controls (no score)

Scoring table

|        |  |
|--------|--|
| ++     | Matches completely/fully fulfilled   |
| +      | Matches incompletely but sufficiently/only partly but sufficiently fulfilled |
| -      | Does not match or matches insufficiently/insufficiently fulfilled            |
| c.b.e. | Cannot be evaluated  |

MDRPA

Checklist for the evaluation of the most relevant studies for building antimicrobial resistance (AMR) outcome trees, healthcare-associated infection (HAI) attributable case fatality and attributable length-of-stay (LOS)

| No                            | First author, year | Study type                       | Sample size  |  | Representativeness |   |   | Matching or controlling for confounders   |  |  |  |   |  | Statistically significant outcome results | Risk difference  |  |   |
|-------------------------------|--------------------|----------------------------------|--|--|--------------------|---|---|---|--|--|--|---|--|---|--|--|---|
|                               |                    |                                  | N (cases,controls)                                       | calculation a priori                                     | Geographical       | Demographical   | Clinical  | Exclusion/inclusion criteria  | Demographics   | Underlying disease   | Infection site   | Hospital and unit/ward                          | Follow-up  |   | Case fatality  | LOS  |   |
|                               |                    |                                  |  |  |                    |   |   |   |  |  |  |   |  |   |  |  |   |
| BSI<br>R vs S                 | 1                  | Score                            | -  | 59 cases<br>88 controls                                  | -                  | ++  | +   | -   | ++   | -  | -  | -   | -  | ++  | ++   | Mort. rate cases=35.8<br>Mort. rate controls=12.5%<br>aOR=4.3; 95%CI(1.67-11.07)   | no data   |
|                               |                    | Comments                         | Retrospective study                                      |  |                    |   | children patients   | children under chemotherapy and HSC transplant  |  |  |  | all BSI   |  | 30 days                                   |  | DR adjusted for gender, type of cancer and neutropenia   |   |
|                               | 2                  | Score                            | -  | 41 cases<br>50 controls                                  | -                  | +   | ++  | -   | ++   | -  | c.b.e  | c.b.e   | -  | ++  | -  | Mort. rate cases=36.6%<br>Mort. rate controls=46%<br>OR=0.68; 95%CI(0.27-1.71)   | no specific data  |
|                               |                    | Comments                         | Retrospective cohort study                               |  |                    |   | transplanted patients   |   | no information   | no information   | all BSI  |   | 28 days  |   |  |  |   |
|                               | 3                  | Score                            | +  | 127 cases<br>582   | -                  | ++  | ++  | ++  | ++   | ++   | ++   | -   | +  | ++  | ++   | Mort. rate cases=17.2%<br>Mort. rate controls=32.3%  | mean±SD<br>cases=31.83±30<br>controls=16.38±18                      |
|                               |                    | Comments                         | Prospective study  |  |                    |   |   |   | not matched but controlled in univariate   | not matched but controlled in univariate   | all BSI  |   | 30 days  |   |  |  |   |
|                               | 4                  | Score                            | -  | a) 25 cases<br>84 controls<br>b) 21 cases<br>21 controls | -                  | +   | ++  | ++  | ++   | ++   | a) ++<br>b) ++   | a) -<br>b) ++                                   | -  | ++  | ++   | I) Mort. rate cases=40%<br>Mort. rate controls=11.9%<br>OR=6.829; 95%CI(1.945-23.984)<br>II) Mort. rate cases=52%<br>Mort. rate controls=9.6%<br>III) Mort. rate cases=56%<br>Mort. rate controls=16.7%<br>IV) c) Mort. rate cases=61.9%<br>Mort. rate controls=9.5% | mean±SD<br>cases=26.4±28.3<br>controls=16.5 ±23.6                   |
|                               |                    | Comments                         | Retrospective cohort study                               | a) whole sample<br>b) matched pairs                      |                    |   |   |   | a) whole sample<br>b) matched pairs<br>group a) was controlled in univariate analyses        | a) whole sample<br>b) matched pairs  | all BSI  |   | I) 30 days<br>II) infection related<br>III) overall mortality<br>IV) matched pairs | all results are significant               | I) 30 days<br>II) infection related<br>III) overall mortality<br>IV) matched pairs   |  |   |
|                               | 5                  | Score                            | -  | 46 cases<br>42 controls                                  | -                  | ++  | ++  | -   | ++   | -  | -  | -   | ++   | -   | -  | Mort. rate cases=42.2%<br>Mort. rate controls=45.2%<br>OR=1.076; 95%CI(0.356-3.254)  | in ICU<br>mean±SD<br>cases=49.3±34.6<br>controls=46.8±32.3          |
| Comments                      |                    | Retrospective cohort study       |  |  |                    | burned patients in ICU  |   |   |  | all BSI  |  | mortality in hospital                           |  |   |  |  |   |
| 6                             | Score              | +                                | 27 cases<br>11 controls                                  | -  | ++                 | ++  | -   | ++  | ++   | ++   | -  | -   | -  | -   | Mort. rate cases=40%<br>Mort. rate controls=9.1%   | no data  |   |
|                               | Comments           | Prospective study                |  |  |                    | patients with hematological malignancies                      |   | not matched but controlled in univariate analyses                                       | not matched but controlled in univariate analyses  | all BSI  |  | 21 days   |  |   |  |  |   |
| 7                             | Score              | -                                | 40 cases<br>66 controls                                  | -  | ++                 | ++  | -   | ++  | -  | -  | -  | -   | -  | ++  | Mort. rate cases=50%<br>Mort. rate controls=24.2%<br>OR=3.31; 95%CI(1.27-8.59)   | mean±SD<br>cases=27±14<br>controls=17±13   |   |
|                               | Comments           | Retrospective case-control study |  |  |                    | patients with BSI and systemic inflammatory response syndrome |   |   |  | all BSI  |  | 21 days   |  |   |  |  |   |
| 8                             | Score              | -                                | 57 cases<br>63 controls                                  | -  | -                  | ++  | ++  | ++  | c.b.e  | c.b.e  | -  | +   | ++   | -   | Mort. rate cases=42.1%<br>Mort. rate controls=41.2%  | mean (range)<br>cases=59 (4-205)<br>controls=62 (3-378)  |   |
|                               | Comments           | Retrospective study              |  |  |                    |   |   | the study considered more resistances and no information was available for the matching | the study considered more resistances and no information was available for the CRAB matching | all BSI  |  | 30 days   |  |   |  |  |   |
| 9                             | Score              | -                                | 42 cases<br>160 controls                                 | -  | +                  | ++  | ++  | ++  | c.b.e  | c.b.e  | -  | +   | ++   | ++  | Mort. rate cases=38.1%<br>Mort. rate controls=21.6%<br>OR=2.20; 95%CI(1.06-4.55)<br>aOR=2.24; 95%CI(0.80-6.29)*                                    | median (IQR)<br>cases=25 (13-38)<br>controls=16 (10-31)  |   |
|                               | Comments           | Retrospective study              |  |  |                    |   |   | the article did not compare cases with controls, instead survivors with non survivors   | the article did not compare cases with controls, instead survivors with non survivors        | all BSI  |  | 30 days   |  |   | adjusted for corticosteroid use, nosocomial acquisition, polymicrobial infection, Charlson's weighted index of co-morbidity, and admission to ICUs |  |   |
| Resp tract<br>R vs S          | 1                  | Score                            | +  | 22 cases<br>46 controls                                  | -                  | ++  | ++  | ++  | ++   | ++   | ++   | -   | +  | ++  | -  | Mort. rate cases=22.7%<br>Mort. rate controls=17.4%  | median (IQR)<br>cases=14(12-21)<br>controls=11(7-16)                |
|                               |                    | Comments                         | Prospective observational study                          |  |                    |   | there are some exclusion criteria for immunosuppressed patients (look fulltext) |   | not matched but controlled in univariate analyses  | not matched but controlled in univariate analyses  | all pneumonia  |   | 30 days  |   |  |  |   |
|                               | 2                  | Score                            | c.b.e  | 50 cases<br>50 controls                                  | -                  | ++  | ++  | -   | ++   | ++   | +  | -   | +  | ++  | ++   | Mort. rate cases=60%<br>Mort. rate controls=28%<br>OR=6.2; 95%CI(1.7-22.1)   | no data   |
|                               |                    | Comments                         | Case-control study                                       | patients with COPD, sputum sample was                    |                    |   | patients with COPD acute exacerbation   |   | matched for age, controls for gender   | matched for degree of airway obstruction   | all resp tract   |   | 2 years  |   |  |  |   |
|                               | 3                  | Score                            | -  | 226 cases<br>31 controls                                 | -                  | ++  | ++  | ++  | ++   | -  | ++   | -   | -  | -   | ++   | Mort. rate cases=44.7%<br>Mort. rate controls=31.7%<br>HR=1.39; 95%CI(1.05-1.83)   | median (IQR)<br>cases=27(14-56.3)<br>controls=25(13-46)             |
|                               |                    | Comments                         | Multicentre retrospective study                          |  |                    |   | EU countries + USA  |   |  |  | not matched but controlled in univariate analyses for Charlson score | all resp tract                                  |  | mortality in hospital                     |  |  |   |
|                               | 4                  | Score                            | -  | 60 cases<br>31 controls                                  | -                  | ++  | ++  | ++  | ++   | +  | +  | -   | +  | -   | -  | a) Mort. rate cases=15%<br>Mort. rate controls=29%<br>b) Mort. rate cases=6%<br>Mort. rate controls=55%  | no data   |
| Comments                      |                    | Retrospective study              |  |  |                    |   |   | not matched but controlled in univariate analyses for gender, age is higher in cases    | not matched but controlled in univariate analyses for Charlson score                         | all resp tract   |  | a) 7 days<br>b) mortality in hospital           |  |   |  |  |   |
| 5                             | Score              | -                                | 42 cases<br>68 controls                                  | -  | ++                 | ++  | +   | ++  | c.b.e  | c.b.e  | -  | +   | -  | ++  | Mort. rate cases=59.5%<br>Mort. rate controls=35.2%<br>OR=2.69; 95%CI(1.14-6.43)   | no data  |   |
|                               | Comments           | Retrospective study              |  |  |                    | ICU patients  |   | no matching and no comparison between cases and controls                                | no matching and no comparison between cases and controls                                     | all resp tract   |  | mortality in ICU                                |  |   |  |  |   |
| 6                             | Score              | +                                | 20 cases<br>55 controls                                  | -  | +                  | ++  | ++  | ++  | ++   | ++   | -  | +   | ++   | -   | Mort. rate cases=35%<br>Mort. rate controls=29%  | median (IQR)<br>cases=37(28-57.2)<br>controls=34(21-47)  |   |
|                               | Comments           | Prospective observational study  |  |  |                    | excluded patients with known risk factors (look at full text) |   | not matched but controlled in univariate analyses                                       | not matched but controlled in univariate analyses  | all resp tract   |  | 28 days   |  |   |  |  |   |
| 7                             | Score              | -                                | a) 14 cases<br>63 controls<br>b) 27 cases<br>64 controls | -  | ++                 | ++  | ++  | ++  | c.b.e  | c.b.e  | -  | +   | -  | -   | a) Mort. rate cases=28.6%<br>Mort. rate controls=23.8%<br>b) Mort. rate cases=7.4%<br>Mort. rate controls=16.5%                                    | Mean ± SD<br>a) cases= 25.8 ± 23.6<br>b) cases=17.5 ± 20.8   |   |
|                               | Comments           | Retrospective study              | a) HAI<br>b) CAI   |  |                    |   |   | cases and controls are not compared, the comparison is between HAI and CAI              | cases and controls are not compared, the comparison is between HAI and CAI                   | all resp tract   |  | mortality in hospital                           |  |   | a) HAI<br>b) CAI   | a) HAI<br>b) CAI   |   |
| Mixed inf.<br>site<br>R vs NI | 1                  | Score                            | ++   | 82 cases<br>82 controls                                  | -                  | ++  | ++  | ++  | ++   | ++   | +  | NA  | ++   | -   | ++   | Mort. rate cases=21%<br>Mort. rate controls=12%<br>OR=4.4  | median<br>cases=20<br>controls=10                                   |
|                               |                    | Comments                         | Matched cohort study                                     |  |                    |   |   |   | not matched but controlled in univariate analyses  | not matched but controlled in univariate analyses for McCabe score   |  |   | mortality in hospital  | only OR                                   |  |  |   |
| 2                             | Score              | ++                               | 34 cases<br>34 controls                                  | -  | ++                 | ++  | +   | ++  | ++   | ++   | NA   | ++  | -  | -   | a) Mort. rate cases=44%<br>Mort. rate controls=47%<br>b) Mort. rate cases=47%<br>Mort. rate controls=50%   | mean SD<br>cases=57.0±37.3<br>controls=46.9±22.5   |   |
|                               | Comments           | Matched case-control study       |  |  |                    | patients in ICU   |   | not matched but controlled in univariate analyses                                       |  |  |  | a) mortality in ICU<br>b) mortality in hospital |  |   | a) mortality in ICU<br>b) mortality in hospital  |  |   |
| Mixed inf.<br>site<br>R vs S  | 1                  | Score                            | -  | 44 cases<br>66 controls                                  | -                  | -   | ++  | ++  | ++   | ++   | -  | -   | +  | -   | ++   | Mort. rate cases=54.5%<br>Mort. rate controls=16.2%  | in ICU<br>mean(SD)<br>cases=21(47.7)<br>controls=11(16.2)           |
|                               |                    | Comments                         | Retrospective cohort study                               | cases are resistant and intermediate                     |                    |   |   |   | not matched but controlled in univariate analyses for gender, age is higher in cases         |  |  |   | mortality in hospital  |   |  |  |   |
|                               | 2                  | Score                            | -  | 20 cases<br>34 controls                                  | -                  | -   | ++  | +   | ++   | -  | -  | -   | ++   | -   | -  | Mort. rate cases=70%<br>Mort. rate controls=58.9%<br>OR=1.6333;<br>95%CI(0.5043-5.2901)<br>Adults:<br>cases=81.3%<br>controls=71.4%<br>paediatric:<br>cases=50.0%  | no specific data  |
|                               |                    | Comments                         | Retrospective cohort study                               |  |                    |   | adults, children and neonates   | patients in ICU   |  |  |  |   | mortality in hospital  |   |  |  |   |
|                               | 3                  | Score                            | -  | 134 cases<br>149 controls                                | -                  | ++  | ++  | ++  | ++   | +  | +  | ++  | +  | -   | ++   | Mort. rate cases=24.6%<br>Mort. rate controls=12.8%<br>OR=1.77; 95%CI(1.41-2.22)   | mean(SD), median<br>cases=25.1(16.1), 20<br>controls=39.0(30.3), 30 |
|                               |                    | Comments                         | Retrospective study                                      |  |                    |   |   |   | not matched but controlled in univariate analyses for age, gender is different               | not matched but controlled in univariate analyses for main diseases, only renal disease is higher in cases | not matched but controlled in univariate analyses                    |   | mortality in hospital  |   |  |  |   |
| 4                             | Score              | -                                | 559 cases<br>7881 controls                               | -  | NA                 | ++  | ++  | ++  | NA   | NA   | NA   | -   | -  | ++  | Mort. rate cases=25-60%<br>Mort. rate controls=7-50%<br>RR=2.34; 95%CI(1.53 - 3.57)  |  |   |
|                               | Comments           | Review and Meta-analyses         |  |  |                    | different countries   |   |   |  |  |  | mortality in hospital                           | significant RR   |   |  |  |   |
| 5                             | Score              | +                                | 18 cases<br>35 controls                                  | -  | ++                 | ++  | +   | ++  | ++   | ++   | ++   | ++  | -  | -   | Mort. rate cases=22%<br>Mort. rate controls=23%  | in ICU<br>median (IQR)<br>cases=10(0-14)<br>controls=10(0-44)  |   |
|                               | Comments           | Prospective study                |  |  |                    | patients in ICU   |   | not matched but controlled in univariate analyses                                       | not matched but controlled in univariate analyses  | not matched but controlled in univariate analyses  |  | mortality in ICU                                |  |   |  |  |   |
| 6                             | Score              | -                                | 188 cases<br>168 controls                                | -  | -                  | ++  | ++  | ++  | c.b.e  | c.b.e  | -  | -   | -  | ++  | Mort. rate cases=26.1%<br>Mort. rate controls=12.5%  | median (range)<br>cases=39(5-597)<br>controls=24(1-262)  |   |
|                               | Comments           | Retrospective study              |  |  |                    |   |   |   |  |  |  |   |  |   |  |  |   |

|   |          |          |                                   |                         |   |   |   |   |   |   |       |   |                       |    |   |  |   |
|---|----------|----------|-----------------------------------|-------------------------|---|---|---|---|---|---|-------|---|-----------------------|----|---|--|---|
|   |          | Comments | Retrospective case-control study  |                         |   |   |   |   | no information available  | no information available  |       |   | mortality in hospital |    |   |  |   |
| 7 | Su, 2016 | Score    | -                                 | 25 cases<br>29 controls | - | - | ++  | - | ++  | c.b.e   | c.b.e | - | -                     | ++ | - | a) Mort. rate cases=36%<br>Mort. rate controls=31.0%<br>b) Mort. rate cases=47.6%<br>Mort. rate controls=37.9% | no specific data  |
|   |          | Comments | Retrospective double centre study |                         |   |   | patients with abdominal organ transplantation |   | no comparison between cases and controls, but between dead patients and not | no comparison between cases and controls, but between dead patients and not |       |   | 30 days               |    |   | a) related mortality<br>b) overall mortality   | no comparison between cases and controls, but between dead patients and not |

Sample size N refers to total number of cases and controls (no score)  
**Calculation a priori:** ++ if performed (e.g. based on expected prevalence or on literature data) or the study refers to large national surveys; - if not performed

**Study type** Study type: ++ matched cohort or case-control studies; + prospective cohort or case-control studies; - retrospective database studies  
**Representativeness** **Geographical:** ++ if the study was conducted in an EU/EEA setting; + if the study was conducted in high-income country (ref. World bank); - if the study was not conducted in an EU/EEA or high-income country setting  
**Demographic:** ++ if the study population represents all age groups; + if the study population represents selected age-specific groups (e.g. elderly, infants); - if the study population represents a selected sex category and age-specific groups  
**Clinical:** ++ if the study population represents the overall hospital population; + if the study population partially represents the hospital population; - if the study population represents a disease-specific population (e.g. liver transplanted patients, cancer patients, etc.)  
**Exclusion/inclusion criteria:** ++ if the same exclusion/inclusion criteria were adopted for both cases and controls; + if some (but not all) exclusion/inclusion criteria were adopted for both cases and controls; - if exclusion/inclusion criteria were different in cases and controls  
**Demographics:** ++ if performed for age and sex; + if performed only for age or only for sex; - if not performed at all  
**Matching or controlling for confounders** **Underlying disease:** ++ if performed for two or more criteria (e.g. comorbidity score, McCabe score, severity index, n. comorbidities, allergy, immunosuppression status, prior hospitalisation etc.); + if performed for only one criteria; - if not performed at all  
**Infection site:** ++ if performed; - if not performed  
**Hospital and unit/ward:** ++ if same hospital and same unit/ward; + if same hospital but different unit/ward; - if not same hospital and/or not same unit/ward  
**Follow-up:** ++ if ≥ 28 days; - if < 28 days  
**Risk difference** **Statistically significant outcome results:** ++ if results and 95%CI are statistically significant; - if results and 95%CI are not statistically significant  
**Case fatality and LOS** refer to risk difference estimates in cases and controls (no score)

Scoring table

|        |   |
|--------|---|
| ++     | Matches completely/is completely fulfilled                                      |
| +      | Matches incompletely but sufficiently/is only partly but sufficiently fulfilled |
| -      | Does not match or matches insufficiently/is insufficiently fulfilled            |
| c.b.e. | Cannot be evaluated   |



| CRPA Checklist for the evaluation of the most relevant studies for building antimicrobial resistance (AMR) outcome trees, healthcare-associated infection (HAI) attributable case fatality and attributable length-of-stay (LOS) |                    |                                 |                                    |  |                    |                                   |          |   |   |   |   |   |   |   |  |   |   |
|--|--------------------|---------------------------------|------------------------------------|--|--------------------|-----------------------------------|----------|---|---|---|---|---|---|---|--|---|---|
| Nr   | Study              | Study type                      | Sample size                        |  | Representativeness |                                   |          | Matching or controlling for confounders |   |   |   |   |   | Risk difference                           |  |   |   |
|  |                    |                                 | N (cases,controls)                 | calculation a priori                             | Geographical       | Demographical                     | Clinical | Exclusion/inclusion criteria            | Demographics  | Underlying disease  | Infection site  | Hospital and unit/ward  | Follow-up   | Statistically significant outcome results | Case fatality  | LOS   |   |
|  | First author, year |                                 |                                    |  |                    |                                   |          |   |   |   |   |   |   |   |  |   |   |
| BSI R vs S   | 1                  | Score                           | -                                  | 55 cases<br>65 controls                          | -                  | -                                 | ++       | ++                                      | ++  | c.b.e   | c.b.e   | -   | +   | ++  | -  | Mort. cases= 47.3%<br>Mort. controls= 36.9%<br>OR=1.53  | mean (range) LOS=43.7 (378)                       |
|  |                    | Comments                        | Retrospective study                |  |                    |                                   |          |   |   | the study considered more resistance and no information was available for the CRAB matching   | the study considered more resistance and no information was available for the CRAB matching | all BSI   |   | 30 days                                   |  |   |   |
|  | 2                  | Score                           | -                                  | 13 cases<br>137 controls                         | -                  | +                                 | ++       | ++                                      | ++  | ++  | ++  | -   | -   | ++  | -  | Mort. cases= 54%<br>Mort. controls= 32%   | no specific data                                  |
|  |                    | Comments                        | Retrospective study                |  |                    |                                   |          |   |   | not matched but controlled in univariate analyses   | not matched but controlled in univariate analyses   | all BSI   | 2 hospitals   | 30 days                                   |  |   |   |
|  | 3                  | Score                           | -                                  | 44 cases<br>156 controls                         | -                  | +                                 | ++       | ++                                      | ++  | c.b.e   | c.b.e   | -   | +   | ++  | ++   | Mort. cases= 39.1%<br>Mort. controls= 21.2%<br>OR=2.40; 95%CI(1.18-4.86)<br>aOR=2.74; 95%CI(1.02-7.37)* | median (IQR) cases=16(14-42)<br>controls=16(9-29) |
|  |                    | Comments                        | Retrospective cohort study         |  |                    |                                   |          |   |   | the article did not compare cases with controls, instead survivors with non   | the article did not compare cases with controls, instead survivors with non                 | all BSI   |   | 30 days                                   |  |   |   |
|  | 4                  | Score                           | -                                  | 28 cases<br>158 controls                         | -                  | +                                 | ++       | ++                                      | ++  | c.b.e   | c.b.e   | -   | +   | ++  | -  | Mort. cases= 53.6%<br>Mort. controls= 35.2%<br>OR=2.216; 95%CI(0.946-4.776)                             | no data   |
|  |                    | Comments                        | Retrospective study                |  |                    |                                   |          |   |   | the information was not specific  | the information was not specific  | all BSI   |   | 30 days                                   |  |   |   |
| 5  | Score              | -                               | 118 cases<br>116 controls          | -  | +                  | ++                                | ++       | ++                                      | c.b.e   | c.b.e   | -   | +   | -   | -   | Mort. cases= 22.0%<br>Mort. controls= 22.4%<br>OR=3.65; 95%CI(0.72-18.67)  | no data   |   |
|  | Comments           | Retrospective study             |                                    |  |                    |                                   |          |   | the article did not compare cases with controls, instead survivors with non survivors | the article did not compare cases with controls, instead survivors with non survivors   | all BSI   |   | 14 days   |   |  |   |   |
| 6  | Score              | +                               | 145 cases<br>487 controls          | ++   | ++                 | ++                                | ++       | ++                                      | +   | ++  | -   | -   | ++  | -   | a) Mort. cases= 13%<br>Mort. controls= 13%<br>b) Mort. cases= 35%<br>Mort. controls= 27%   | no data   |   |
|  | Comments           | Prospective multicentre study   |                                    |  |                    |                                   |          |   | not matched but controlled in univariate analyses for age, gender is different        | not matched but controlled in univariate analyses for SAPS score, Charlson index and main diseases. Only immunosuppressive therapy is higher in cases | all BSI   | 10 hospitals  | a) 48h<br>b) 30 days  |   |  |   |   |
| 7  | Score              | -                               | 33 cases<br>88 controls            | -  | ++                 | ++                                | ++       | ++                                      | c.b.e   | ++  | -   | +   | ++  | -   | a) Mort. cases= 46%<br>Mort. controls= 36%<br>b) Attrib. mort. cases=33%<br>Attrib. mort. controls=30%<br>OR=1.8; 95%CI(0.6-6.8) | mean (range) cases=19(2-98)<br>controls=9(2-56)   |   |
|  | Comments           | Retrospective cohort study      |                                    |  |                    |                                   |          |   | the article did not compare cases with controls, instead survivors with non survivors | not matched but controlled in univariate analyses   | all BSI   |   | a) 30 days<br>b) 7 days (defined as attributable mortality) |   |  |   |   |
| 8  | Score              | c.b.e                           | 29 cases<br>48 controls            | -  | -                  | ++                                | ++       | ++                                      | ++  | ++  | -   | +   | ++  | -   | Mort. cases= 54.2%<br>Mort. controls= 44.8%<br>OR=0.68; 95%CI(0.27-1.73)   | mean±SD cases=43±31.7<br>controls=43.1±31.2   |   |
|  | Comments           | Case-control study              |                                    |  |                    |                                   |          |   | not matched but controlled in univariate analyses                                     | not matched but controlled in univariate analyses for main comorbidities  | all BSI   |   | 30 days   |   |  |   |   |
| Recsp tract R vs S   | 1                  | Score                           | +                                  | 68 cases*<br>101 controls                        | -                  | ++                                | ++       | +                                       | ++  | ++  | ++  | -   | ++  | -   | Mort. cases= 37%<br>Mort. controls= 31%  | median (IQR) cases=29(19-46)<br>controls=29(19-46)  |   |
|  |                    | Comments                        | Prospective observational study    |  |                    |                                   |          | ICU patients                            |   | not matched but controlled in univariate analyses   | not matched but controlled in univariate analyses   | all Resp tract  | ICU   | mortality during ICU stay                 |  |   |   |
| Mixed inf. site R vs NI  | 1                  | Score                           | -                                  | 58 resistant<br>125 sensitive<br>57 non infected | -                  | +                                 | ++       | ++                                      | ++  | a) ++<br>b) +   | a) ++<br>b) ++  | -   | ++  | -   | Mort. resist= 31%<br>Mort. sensit= 15%<br>Mort. control=9%   | median(IQR) resist=30(15-70)<br>sensit=16(6-33)<br>control=10(6-17)                                     |   |
|  |                    | Comments                        | Retrospective case-control study   |  |                    |                                   |          |   | not matched but controlled in univariate analyses                                     | not matched but controlled in univariate analyses   | a) R vs S<br>b) R vs NI (only gender)   | a) R vs S, except congestive heart failure<br>b) R vs NI, except COPD |   | mortality in hospital                     |  |   |   |
| Mixed inf. site R vs S   | 1                  | Score                           | -                                  | 32 cases<br>350 controls                         | -                  | +                                 | ++       | ++                                      | ++  | ++  | -   | -   | +   | ++  | Mort. cases= 27%<br>Mort. controls= 8.9%<br>OR=2.89; 95%CI(1.15-7.28)  | median (IQR) cases=14(8-29)<br>controls=9(5-15)   |   |
|  |                    | Comments                        | Retrospective observational cohort |  |                    |                                   |          |   |   | not matched but controlled in univariate analyses   |   |   |   | mortality in hospital                     |  |   |   |
|  | 2                  | Score                           | -                                  | 135 cases<br>719 controls                        | -                  | +                                 | ++       | ++                                      | ++  | -   | -   | -   | +   | ++  | Mort. cases= 31.1%<br>Mort. controls= 16.7%<br>OR=1.80; 95%CI(1.38-2.51)   | median (IQR) cases=11(1-41)<br>controls=11(1-15)  |   |
|  |                    | Comments                        | Retrospective cohort study         |  |                    |                                   |          |   |   |   |   |   |   | mortality in hospital                     |  |   |   |
|  | 3                  | Score                           | -                                  | 253 cases<br>2289 controls                       | -                  | +                                 | ++       | ++                                      | ++  | -   | -   | -   | -   | ++  | Mort. cases= 17.4%<br>Mort. controls= 13.4%<br>RR=1.39; 95%CI(1.09-1.76)   | prior isolation median (IQR) cases=8(4-12)<br>controls=4(4-9)   |   |
|  |                    | Comments                        | Retrospective cohort study         |  |                    |                                   |          |   |   |   |   |   |   | mortality in hospital                     |  |   |   |
|  | 4                  | Score                           | -                                  | 82 cases<br>82 controls                          | -                  | +                                 | ++       | ++                                      | ++  | ++  | ++  | -   | -   | -   | -  | Mort. cases= 22.0%<br>Mort. controls= 19.5%   | no data   |
| Comments   |                    | Retrospective study             |                                    |  |                    |                                   |          |   | not matched but controlled in univariate analyses                                     | not matched but controlled in univariate analyses   |   |   | mortality in hospital                                       |   |  |   |   |
| 5  | Score              | -                               | 16 studies                         | -  | NA                 | ++                                | ++       | ++                                      | ++  | NA  | NA  | -   | -   | c.b.e                                     | ++   | Cross OR=1.64; 95%CI(1.40, 1.93)<br>adjusted OR=2.30; 95%CI(1.53, 3.51)                                 | no data   |
|  | Comments           | Meta-analyses                   |                                    |  |                    | articles from different countries |          |   |   |   |   |   | different in the different articles                         |   |  |   |   |
| 6  | Score              | +                               | 15 cases<br>65 controls            | -  | -                  | ++                                | ++       | ++                                      | ++  | ++  | -   | -   | -   | -   | Mort. cases= 13.34%<br>Mort. controls= 1.53%   | no data   |   |
|  | Comments           | Prospective observational study |                                    |  |                    |                                   |          |   | not matched but controlled in univariate analyses                                     | not matched but controlled in univariate analyses   |   |   | mortality in hospital                                       |   |  |   |   |
| 7  | Score              | ++                              | 10 cases<br>10 controls            | -  | +                  | ++                                | ++       | ++                                      | +   | ++  | ++  | -   | -   | -   | Mort. cases= 20%<br>Mort. controls= 10%  | median preinfection cases=12<br>controls=15<br>postinfection cases=33.5<br>controls=20                  |   |
|  | Comments           | Matched case-control study      |                                    |  |                    |                                   |          |   | matched for age   |   |   |   | mortality in hospital                                       |   |  |   |   |

Sample size N refers to total number of cases and controls (no score)  
Calculation a priori: ++ if performed (e.g. based on expected prevalence or on literature data) or the study refers to large national surveys; - if not performed

Study type Study type: ++ matched cohort or case-control studies; + prospective cohort or case-control studies; - retrospective database studies

Representativeness

Geographical: ++ if the study was conducted in an EU/EEA setting; + if the study was conducted in high-income country(ies); - if the study was not conducted in an EU/EEA or high-income country setting

Demographical: ++ if the study population represents all age groups; + if the study population represents selected age-specific groups (e.g. elderly, infants); - if the study population represents a selected sex category and age-specific groups

Clinical: ++ if the study population represents the overall hospital population; + if the study population partially represents the hospital population; - if the study population represents a disease-specific population (e.g. liver transplanted patients, cancer patients, etc.)

Exclusion/inclusion criteria: ++ if the same exclusion/inclusion criteria were adopted for both cases and controls; + if some (but not all) exclusion/inclusion criteria were adopted for both cases and controls; - if exclusion/inclusion criteria were different in cases and controls

Demographics: ++ if performed for age and sex; + if performed for age or only for sex; - if not performed at all

Underlying disease: ++ if performed for two or more criteria (e.g. comorbidity score, McCabe score, severity index, n. comorbidities, allergy, immunosuppression status, prior hospitalisation etc.); + if performed for only one criteria; - if not performed at all

Infection site: ++ if performed; - if not performed

Hospital and unit/ward: ++ if same hospital and same unit/ward; + if same hospital but different unit/ward; - if not same hospital and/or not same unit/ward

Follow-up: ++ if ≥ 28 days; - if < 28 days

Statistically significant outcome results: ++ if results and 95%CI are statistically significant; - if results and 95%CI are not statistically significant

Case fatality and LOS refer to risk difference estimates in cases and controls (no score)

Scoring table

|        |  |
|--------|--|
| ++     | Matches completely/fully fulfilled   |
| +      | Matches incompletely but sufficiently/only partly but sufficiently fulfilled |
| -      | Does not match or matches insufficiently/insufficiently fulfilled            |
| c.b.e. | Cannot be evaluated  |

| MERSA Checklist for the evaluation of the most relevant studies for building antimicrobial resistance (AMR) outcome trees, healthcare-associated infection (HAI) attributable case fatality and attributable length-of-stay (LOS) |                    |                        |   |   |   |   |                    |                    |  |   |   |   |  |  |  |   |  |   |   |
|---|--------------------|------------------------|---|---|---|---|--------------------|--------------------|--|---|---|---|--|--|--|---|--|---|---|
| Nr  | Study              | Study type             | Infection type  | Sample size   |   | Representativeness                                    |                    |                    | Matching or controlling for confounders          |   |   |   |  | Risk difference  |  |   |  |   |   |
|   |                    |                        |   | N (cases,controls)  | calculation a priori  | Geographical  | Demographical      | Clinical           | Exclusion/Inclusion criteria                     | Demographics  | Underlying disease  | Infection site  | Hospital and unit/ward   | Follow-up  | Statistically significant outcome results          | Case fatality   | LOS  |   |   |
|   | First author, year |                        | HCA; CA; Mix; c.b.e                                       |   | □ ++; □ +; □ c.b.e  | □ ++; □ +; □ c.b.e                                    | □ ++; □ +; □ c.b.e | □ ++; □ +; □ c.b.e | □ ++; □ +; □ c.b.e                               | □ ++; □ +; □ c.b.e  | □ ++; □ +; □ c.b.e  | □ ++; □ +; □ c.b.e  | □ ++; □ +; □ c.b.e   | □ ++; □ +; □ c.b.e   | □ ++; □ +; □ c.b.e                                 | %; RR; OR; aHR; etc   | (days)   |   |   |
| BSI R vs NI   | 1                  | Atmaca, 2014           | Score   | c.b.e   | c.b.e   | 99 cases<br>99 controls                               | +                  | -                  | ++   | +   | ++  | ++  | ++   | -  | ++   | c.b.e   | ++   | Mort. rate cases= 47.5%<br>Mort. rate controls=29.3%<br>median cases=59<br>controls=8                 |   |
|   |                    | Comments               | Nested case control study                                 | full-text in turkish, data extracted from abstracted in english               |   |   |                    |                    |  | patients in infectious disease unit   |   | not matched but controlled in univariate analyses   | not matched but controlled in univariate analyses                | all BSI  | mortality in hospital                              |   |  | data extracted from original paper in Turkish with help of google translate                           | data extracted from original paper in Turkish with help of google translate                   |
| BSI R vs NI   | 2                  | McMaster, 2015         | Score   | +   | HCA*  | 58 cases*<br>174 controls<br>(231 cases**)            | -                  | ++                 | ++   | +   | ++  | ++  | -  | ++   | ++   | -   | a) Mort. rate cases= 19%<br>Mort. rate controls=21.2%<br>b) Mort. rate cases= 32%<br>Mort. rate controls=34.5%<br>(Mort. rate cases**= 42.9%)  | in ICU median (range) cases=16.6 (1.5-124.1)<br>controls=16.9 (1.9-92.1)<br>(cases**=2.9 (0.4-497.2)) |   |
|   |                    | Comments               | Prospective study   | not explicit in the paper but most probably all HCA                           | * infection acquired in ICU<br>** infection acquired before ICU admission |   |                    |                    |  | all ICU patients  |   | cases acquires in ICU (*) were matched with controls  | cases acquires in ICU (*) were matched with controls (APACHE II) | all BSI  | a) hospitaliz<br>b) 180 days                       | a) hospitaliz<br>b) 180 days  |  | * infection acquired in ICU<br>** infection acquired before ICU admission                             | * infection acquired in ICU<br>** infection acquired before ICU admission                     |
| BSI R vs NI   | 1                  | Stewardson, 2016       | Score   | -   | Mix   | 163 resistant<br>895 sensitive<br>604797 NI           | ++                 | ++                 | ++   | +   | -   | -   | -  | -  | c.b.e  | ++  | Mort. rate resistant=22.1%<br>Mort. rate sensitive=6.8%<br>Mort. rate NI=1.7%<br>R vs NI: HR=3.81/2.61/2.42<br>R vs S: HR=1.19/1.20/1.26   | no specific data, see full-text for modelling values*   |   |
|   |                    | Comments               | Multicentre retrospective cohort study                    | HC onset: 38% cases, 51% controls<br>community onset: 62% cases, 49% controls |   |   |                    |                    |  | patients with acute-care episodes lasting more than one day                                       |   | no univariate analyses, matched in model 2  | no univariate analyses   | all BSI or NI  | mortality in hospital                              | only R vs NI  |  | * the study models the excess in LOS and mortality between groups proposing 3 models for each         | * the study models the excess in LOS and mortality between groups proposing 3 models for each |
|   | 2                  | Yasmin, 2016           | Score   | -   | Mix   | 118 resistant<br>145 sensitive<br>116 NI              | -                  | +                  | ++   | ++  | ++  | ++  | -  | +  | c.b.e  | -   | a) Mort. rate resist= 22%<br>Mort. rate sensit=19.5%<br>Mort. rate NI=1.7%<br>b) Mort. rate resist=19.5%<br>Mort. rate sensit=10.3%  | no specific data  |   |
| BSI R vs S  | 1                  | De la Calle, 2016      | Score   | -   | Mix   | 42 cases<br>56 controls                               | -                  | ++                 | ++   | ++  | ++  | +   | +  | -  | ++   | -   | a) Mort. rate cases= 40.5%<br>Mort. rate controls=37.5%  | no data   |   |
|   |                    | Comments               | Retrospective study                                       | similar HCA/CA between cases and control, but no specific info                | all patients had bacteremic pneumonia with a positive BSI                 |   |                    |                    |  |   | not matched but controlled in univariate analyses for gender, while age was higher in the cases | not matched but controlled in univariate analyses for gender, while age was higher in the cases | all BSI  | a) 30 days<br>b) related mortality (patient died without a definitive infection control) |  |   |  |   |   |
| BSI R vs S  | 2                  | De Rosa, 2016          | Score   | -   | c.b.e   | 106 cases<br>83 controls                              | -                  | ++                 | ++   | ++  | ++  | -   | -  | +  | -  | c.b.e   | Mort. rate cases= 17.9%<br>Mort. rate controls=14.3%   | no data   |   |
|   |                    | Comments               | Retrospective study                                       | no information available  |   |   |                    |                    |  |   |   |   |  | all BSI  | 21 days  | no information available  |  |   |   |
| BSI R vs S  | 3                  | Deodhars, 2015         | Score   | +   | c.b.e   | 40 cases<br>61 controls                               | -                  | -                  | ++   | ++  | ++  | c.b.e   | c.b.e  | -  | +  | c.b.e   | Mort. rate cases= 21%<br>Mort. rate controls=21.3%   | no data   |   |
|   |                    | Comments               | Prospective study   | most probably all HCA   |   |   |                    |                    |  | patients >12 years  |   | no matching and the control is for died vs survived   | no matching and the control is for died vs survived              | all BSI  | mortality in hospital                              |   |  |   |   |
| BSI R vs S  | 4                  | Dolapo, 2014           | Score   | -   | HCA   | 10 cases<br>31 controls<br>b) 64 cases<br>51 controls | -                  | +                  | +  | +   | ++  | c.b.e   | c.b.e  | -  | ++   | -   | a) Mort. rate cases= 0%<br>Mort. rate controls=0.8%<br>b) Mort. rate cases= 15.7%<br>Mort. rate controls=5.2%  | mean±SD<br>a) cases=80.6±42.4<br>b) cases=87.4±40.6<br>c) cases=53.6±36.6<br>controls=55.7±30.2       |   |
|   |                    | Comments               | Retrospective study                                       | not specified in the article but patients are neonates in ICU                 | a) period A (2000-2003)<br>b) period B (2004-2009)                        | neonates patients                                     | patients in NICU   |                    | no matching and no control for cases vs controls | no matching and no control for cases vs controls  | all BSI   | 14 days   | no information available   | a) period A (2000-2003)<br>b) period B (2004-2009)                                       | a) period A (2000-2003)<br>b) period B (2004-2009) |   |  |   |   |
| BSI R vs S  | 5                  | Fortuin de Smidt, 2015 | Score   | +   | Mix   | 86 cases<br>154 controls                              | -                  | -                  | ++   | ++  | ++  | ++  | +  | -  | c.b.e  | ++  | Mort. rate cases= 29.1%<br>Mort. rate controls=14.3%   | median (IQR)<br>cases=38 (14-64)<br>controls=19 (7-33)  |   |
|   |                    | Comments               | Prospective cross-sectional study                         | HCA: 70% cases, 50% controls<br>CA: 24% cases, 49% controls                   |   |   |                    |                    |  |   | not matched but controlled in univariate analyses   | not matched but controlled for Pitt bacteremia score  | all BSI  | mortality in hospital  |  |   |  |   |   |
| BSI R vs S  | 6                  | Kim D.H, 2014          | Score   | -   | c.b.e   | 29 cases<br>8 controls                                | -                  | +                  | ++   | -   | ++  | c.b.e   | c.b.e  | -  | +  | c.b.e   | ++   | Mort. rate cases= 62%<br>Mort. rate controls=0%<br>OR=0.156; 95%CI(0.047-0.534)                       | no specific data  |
|   |                    | Comments               | Retrospective study                                       | no information available  |   |   |                    |                    |  | patients had Cardiac Implanted Electronic Device-Related Infective Endocarditis (CIED-related IE) |   | no matching and no control for cases vs controls  | no matching and no control for cases vs controls                 | all BSI  | mortality in hospital                              |   |  |   |   |
| BSI R vs S  | 7                  | Kobayashi, 2014        | Score   | -   | c.b.e   | 151 cases<br>189 controls                             | -                  | +                  | ++   | ++  | ++  | c.b.e   | c.b.e  | -  | +  | c.b.e   | Mort. rate cases= 39.7%<br>Mort. rate controls=30.7%   | no data   |   |
|   |                    | Comments               | Retrospective study                                       | no information available  |   |   |                    |                    |  |   | no matching and no control for cases vs controls  | no matching and no control for cases vs controls  | all BSI  | 90 days  | no information available                           |   |  |   |   |
| BSI R vs S  | 8                  | Lee J.Y, 2014          | Score   | c.b.e   | CA  | 31 cases<br>138 controls                              | -                  | +                  | ++   | ++  | ++  | ++  | ++   | -  | ++   | -   | 1-a) Mort. rate cases= 3.2%<br>Mort. rate controls=3.6%<br>1-b) Mort. rate cases= 5.5%<br>Mort. rate controls=13.8%<br>1-c) Mort. rate cases= 16.1%<br>Mort. rate controls=19.6%<br>2-a) Mort. rate cases= 0%<br>Mort. rate controls=3.6%<br>2-b) Mort. rate cases= 3.2%<br>Mort. rate controls=9.4%<br>2-c) Mort. rate cases= 6.5%<br>Mort. rate controls=13% | median (IQR)<br>cases=47 (19-87)<br>controls=24 (14-44.5)   |   |
|   |                    | Comments               | Cohort study (with prospective and retrospective studies) |   |   |   |                    |                    |  |   | not matched but controlled in univariate analyses   | not matched but controlled in univariate analyses   | all BSI  | a) 1 week<br>b) 30 days<br>c) 12 weeks   | none of the results is significant                 | 1-a/b/c) all-case mortality<br>2-a/b/c) infection related mortality |  |   |   |
| BSI R vs S  | 9                  | Manandhar, 2016        | Score   | -   | c.b.e   | 15 cases<br>21 controls                               | -                  | +                  | ++   | ++  | ++  | +   | ++   | -  | ++   | -   | a) Mort. rate cases= 26.7%<br>Mort. rate controls=36.1%<br>OR=0.62; 95%CI(0.15-2.61)<br>b) Mort. rate cases= 26.7%<br>Mort. rate controls=42.9%<br>OR=0.51; 95%CI(0.12-2.14)   | no specific data  |   |
|   |                    | Comments               | Retrospective study                                       | no information available  |   |   |                    |                    |  | all patients had BSI and UTI  |   | not matched but controlled in univariate analyses for gender                                    | not matched but controlled in univariate analyses                | all BSI  | a) 30 days<br>b) 90 days                           |   | a) 30 days<br>b) 90 days   |   |   |
| BSI R vs S  | 10                 | McMullan, 2016         | Score   | +   | Mix   | 142 cases<br>931 controls                             | -                  | +                  | +  | ++  | ++  | +   | -  | -  | ++   | -   | a) Mort. rate cases= 3.5%<br>Mort. rate controls=2.5%<br>b) Mort. rate cases= 4%<br>Mort. rate controls=4.1%   | median (IQR)<br>cases=17 (8-38)<br>controls=14 (7-33)   |   |
|   |                    | Comments               | Prospective study   | HCA: 48.6% cases, 51.7% controls<br>CA: 51.4% cases, 48.3% controls           |   |   |                    |                    |  | pediatric patients <18 years  |   | not matched but controlled in univariate analyses for gender                                    |  | all BSI  | a) 7 days<br>b) 30 days                            | a) 7 days<br>b) 30 days   |  |   |   |
| BSI R vs S  | 11                 | Nagao, 2016            | Score   | -   | Mix   | 199 cases<br>278 controls                             | -                  | +                  | ++   | ++  | ++  | c.b.e   | c.b.e  | -  | +  | -   | Mort. rate cases= 9%<br>Mort. rate controls=5.8%   | no data   |   |
|   |                    | Comments               | Retrospective study                                       | HCA: total=70.2%<br>CA: total=29.8%   |   |   |                    |                    |  |   | no matching and no control for cases vs controls  | no matching and no control for cases vs controls  | all BSI  | 30 days  |  |   |  |   |   |
| BSI R vs S  | 12                 | Naidoo, 2013           | Score   | -   | Mix   | 85 cases<br>270 controls                              | -                  | -                  | +  | ++  | ++  | +   | -  | -  | ++   | ++  | MRSA OR (95%CI)<br>univariate=3.71 (1.77-7.78)<br>multivariate=3.76 (1.12-12.67)   | no specific data  |   |
|   |                    | Comments               | Retrospective study                                       | HCA: total=49%<br>CA: total=51%   |   |   |                    |                    |  | pediatric patients <13 years  |   | not matched but controlled in univariate analyses for gender, age (in months) was different     |  | all BSI  | mortality in hospital                              |   |  | the mortality was not available in %  |   |
| BSI R vs S  | 13                 | Ong, 2013              | Score   | -   | Mix   | 76 cases<br>353 controls                              | -                  | +                  | ++   | ++  | ++  | -   | -  | -  | ++   | -   | Mort. rate cases= 63%<br>Mort. rate controls=39%<br>HR=1.37; 95%CI(0.95-1.97)  | no data   |   |
|   |                    | Comments               | Retrospective study                                       | HCA: total=57%<br>CA: total=42%   |   |   |                    |                    |  |   |   |   |  | all BSI  | 1 year   |   |  | the study aimed the log-term survival rate  |   |
| BSI R vs S  | 14                 | Park, 2013             | Score   | -   | c.b.e   | 191 cases<br>476 controls                             | -                  | c.b.e              | +  | -   | ++  | NA  | NA   | -  | -  | ++  | OR fixed= 2.33; 95%CI(1.42-3.82)   | no data   |   |
|   |                    | Comments               | Review and meta-analysis                                  | no information available  |   |   |                    |                    |  | papers from different countries   | patients are children and neonates  | endocarditis was in searching criteria  |  | all BSI  | mortality in hospital                              |   |  |   |   |
| BSI R vs S  | 15                 | Simsek, 2014           | Score   | -   | HCA   | 13 cases<br>47 controls                               | -                  | -                  | ++   | -   | ++  | c.b.e   | c.b.e  | -  | +  | ++  | Mort. rate cases= 49%<br>Mort. rate controls=15%<br>OR=12.117; 95%CI(3.159-46.475)   | no specific data  |   |
|   |                    | Comments               | Retrospective study                                       | not specified in the article but very specific patients                       |   |   |                    |                    |  | patients with poststerotomy mediastinitis   |   | no matching and no control for cases vs controls  | no matching and no control for cases vs controls                 | all BSI  | mortality in hospital                              |   |  |   |   |

|                         |                 |                |  |   |   |  |  |  |  |   |   |  |  |                           |       |       |  |  |  |
|-------------------------|-----------------|----------------|--|---|---|--|--|--|--|---|---|--|--|---------------------------|-------|-------|--|--|--|
| 16                      | Thaden, 2015    | Score          | -  | HCA   | 1) 567 cases<br>2047 controls<br>2) 280 cases<br>445 controls     | -  | +  | +  | +  | ++  | c.b.e   | c.b.e  | -  | -                         | ++    | c.b.e | 1-a) Mort. rate cases= 3%;<br>Mort. rate controls=4%;<br>1-b) Mort. rate cases= 8%;<br>rate controls=8%;<br>1-c) Mort. rate cases= 1%;<br>rate controls=10%;<br>2-a) Mort. rate cases= 4%;<br>rate controls=2%;<br>2-b) Mort. rate cases= 9%;<br>rate controls=3%;<br>2-c) Mort. rate cases= 2%;<br>rate controls=4% | no data  |  |
|                         |                 | Comments       | Retrospective study                      | not specified in the article but very specific patients   | 1) with adequate therapy<br>2) with inadequate therapy            | patients are infants in NICU   | patients in NICU   | no matching, and comparison between adequate and inadequate therapy  | no matching, and comparison between adequate and inadequate therapy  | all BSI   | a) 7 days<br>b) 30 days<br>c) hospitaliz  | comparison between adequate and inadequate therapy       | 1) with adequate therapy<br>2) with inadequate therapy<br>a) 7 days<br>b) 30 days<br>c) hospitaliz |                           |       |       |  |  |  |
| 17                      | Theodorou, 2013 | Score          | -  | Mix   | 33 cases<br>41 controls   | -  | ++   | ++   | -  | ++  | ++  | -  | -  | -                         | c.b.e | -     | Mort. rate cases= 33.3%<br>Mort. rate controls=24.4%<br>OR=1.55, 95%CI(0.56-4.28)  | median cases=28.5<br>controls=21   |  |
|                         |                 | Comments       | Retrospective cohort study               | HCA: 89.2%<br>no other info   |   | burned patients in ICU   |  | not matched but controlled in univariate analyses  |  | all BSI   | mortality in hospital   |  |  |                           |       |       |  |  |  |
| 18                      | Wang, 2015      | Score          | -  | Mix   | a) 101 cases<br>b) 59 cases<br>c) 35 cases<br>169 controls        | -  | -  | ++   | ++   | ++  | c.b.e   | c.b.e  | -  | -                         | c.b.e | ++    | a) Mort. rate cases= 47.5%<br>OR=2.249, 95%CI(1.188-4.259);<br>b) Mort. rate cases= 30.5%<br>OR=0.995, 95%CI(0.453-2.200);<br>c) Mort. rate cases=35.3%<br>OR=1.223, 95%CI(0.466-3.210)<br>Rate controls=26.3%<br>Total MRSA OR=1.707  | no data  |  |
|                         |                 | Comments       | Retrospective cohort study               | separated by infection type   | a) HA-MRSA<br>b) CA-MRSA<br>c) unclassified-MRSA                  |  |  | not matched and the comparison results are not understandable  | not matched and the comparison results are not understandable  | all BSI   | mortality in hospital   | only OR HA-MRSA and Total MRSA OR                        | b) HA-MRSA<br>c) CA-MRSA<br>d) unclassified-MRSA   |                           |       |       |  |  |  |
| 19                      | Yaw, 2014       | Score          | -  | Mix   | 185 cases<br>397 controls   | -  | +  | ++   | ++   | ++  | +   | +  | -  | +                         | ++    | ++    | a) Mort. rate cases= 15%<br>Mort. rate controls=12%<br>b) Mort. rate cases= 28%<br>Mort. rate controls=19%<br>c) Mort. rate cases= 75%<br>Mort. rate controls=62%  | no data  |  |
|                         |                 | Comments       | Retrospective observational cohort study | HCA: 90% cases,<br>75% controls<br>CA: 10% cases,<br>25% controls   |   |  |  | not matched but controlled in univariate analyses for gender   | not matched but controlled in univariate analyses for Charlson index, SAPS score is different                            | all BSI   | a) 8 days<br>b) 30 days<br>c) follow up at 01/03/2013                                   | significant only b) and c)                               | a) 8 days<br>b) 30 days<br>c) follow up at 01/03/2013  |                           |       |       |  |  |  |
| 20                      | Yilmaz, 2016    | Score          | +  | Mix   | 100 cases<br>145 controls   | -  | -  | ++   | ++   | ++  | c.b.e   | c.b.e  | -  | -                         | ++    | -     | Mort. rate cases= 22%;<br>Mort. rate controls=11.7%<br>HR=0.99, 95%CI(0.33-3.0)  | no data  |  |
|                         |                 | Comments       | Prospective multicentre study            | HCA: 95% cases,<br>30% controls<br>CA: 5% cases,<br>70% controls  |   |  |  | no matching and no control for cases vs controls   | no matching and no control for cases vs controls   | all BSI   | 28 days   |  |  |                           |       |       |  |  |  |
| Bone R vs S             | 1               | Shoji, 2016    | Score                                    | -   | Mix   | 16 cases<br>55 controls  | -  | +  | ++   | -   | ++  | ++   | +  | -                         | -     | c.b.e | ++   | Mort. rate cases= 25%<br>Mort. rate controls=5.5%  | no data  |
|                         |                 |                | Comments                                 | Retrospective study   | Hosp onset: 37.5% cases,<br>27.3% controls<br>no further info     |  | patients with vertebral osteomyelitis  |  | not matched but controlled in univariate analyses. Differences in age > 65 years   | not matched but controlled for main diseases. Differences only in diabetes mellitus | all vertebrae   | mortality in hospital                                    |  |                           |       |       |  |  |  |
| Skin Wound R vs S       | 1               | Alizadeh, 2014 | Score                                    | c.b.e   | c.b.e   | 82 cases<br>32 controls  | -  | -  | ++   | -   | ++  | +  | -  | -                         | ++    | c.b.e | NA   | no deaths reported in any group  | no data  |
|                         |                 |                | Comments                                 | Cross-sectional study   | no information available  |  | patients with cutaneous lesions  |  | not matched but controlled in univariate analyses for gender, age distribution was different                             | underlying conditions were different in the two groups                              | all skin wound infections   | mortality in hospital                                    |  |                           |       |       |  |  |  |
| Mixed inf. site R vs NI | 1               | Balm, 2013     | Score                                    | -   | HCA   | 121 cases<br>716 controls  | -  | +  | ++   | ++  | ++  | -  | -  | -                         | +     | ++    | ++   | a) Mort. rate cases= 16.5%<br>Mort. rate controls=4.6%<br>OR=5.49, 95%CI(2.75-10.95)<br>b) Mort. rate cases= 28.9%<br>Mort. rate controls=12.5%<br>OR=2.94, 95%CI(1.78-4.85) | no data  |
|                         |                 |                | Comments                                 | Retrospective cohort study  | All patients were negative to infection when admitted to the hosp | cases had clinical MRSA infection controls were only colonized with MRSA (nasal swab)  |  |  | not matched and not controlled   | not matched and not controlled  |   | a) 30 days<br>b) 6 months                                | Both ORs, no information on mortality rates comparison   | a) 30 days<br>b) 6 months |       |       |  |  |  |
|                         |                 |                | Score                                    | ++  | HCA   | a) 3599 cases<br>36614 controls<br>b) 3592 cases<br>3592 controls                      | -  | +  | ++   | ++  | ++  | ++   | ++   | ++                        | +     | ++    | ++   | a) aHR=1.420, 95%CI(1.322-1.525);<br>b) aHR=1.370, 95%CI(1.231-1.524)  | mean a) cases=22.4<br>controls=5.3<br>b) cases=20.1<br>controls=23.2 |
| 2                       | Nelson, 2015    | Comments       | Retrospective matched cohort study       | a) full cohort<br>b) propensity score matched<br>Paper studies the mortality post hosp discharge          |   |  | propensity score matching  | propensity score matching  |  | 1 year after discharge  |   |  |  |                           |       |       |  |  |  |
|                         |                 | Score          | ++                                       | HCA   | a) 745 cases<br>17649 controls<br>b) 737 cases<br>737 controls    | -  | +  | ++   | ++   | ++  | ++  | ++   | ++   | -                         | -     | c.b.e | ++   | a) Mort. rate cases= 8.2%;<br>Mort. rate controls=5.7%<br>b) Mort. rate cases= 8%;<br>rate controls=7%   | mean a) cases=12.8<br>controls=7.6<br>b) cases=11.9<br>controls=9.1  |
| 3                       | Tran, 2016      | Comments       | Retrospective matched cohort study       | a) pre-match cohort<br>b) post-match cohort   |   |  | propensity score matching  | propensity score matching  |  | mortality in hospital   | only a) was significant   | a) pre-match cohort<br>b) post-match cohort              | a) pre-match cohort<br>b) post-match cohort  |                           |       |       |  |  |  |
|                         |                 | Score          | -  | c.b.e   | 1063 cases<br>2825 controls                                       | -  | +  | +  | +  | ++  | ++  | ++   | -  | -                         | ++    | -     | a) Mort. rate cases= 11.9%<br>Mort. rate controls=9.6%<br>RR=1.19, 95%CI(0.96-1.49)<br>b) Mort. rate cases= 3.8%<br>Mort. rate controls=3.8%<br>RR=0.90, 95%CI(0.65-1.24)<br>c) Mort. rate cases= 8.7%<br>Mort. rate controls=7.2%<br>RR=1.15, 95%CI(0.90-1.46)  | both groups=64   |  |
| Mixed inf. site R vs S  | 1               | Ericson, 2015  | Comments                                 | Multicentre retrospective study   | no information available  | invasive infection; indurated blood, cerebrospinal fluid, abscesses, and sterile sites | patients were infants  | patients in NICU   | not matched but controlled in univariate analyses  |   | a) before discharge<br>b) 7 days<br>c) 30 days  | a) before discharge<br>b) 7 days<br>c) 30 days           |  |                           |       |       |  |  |  |
|                         |                 |                | Score                                    | -   | c.b.e   | 71 cases<br>23 controls  | -  | -  | ++   | +   | ++  | +  | -  | -                         | ++    | c.b.e | c.b.e  | Mort. rate cases= 33.8%<br>Mort. rate controls=52.17%  | median (IQR) cases=20 (20)<br>controls=19 (17)                       |
| 2                       | Gimenes, 2016   | Comments       | Retrospective study                      | no information available  |   | patients in ICU  |  | not matched but controlled in univariate analyses for age, gender was different                                |  | mortality in hospital   | no comparison between rates Kaplan Meier survival curve was not significantly different |  |  |                           |       |       |  |  |  |
|                         |                 | Score          | +  | Mix   | 303 cases<br>357 controls   | -  | +  | ++   | ++   | ++  | c.b.e   | c.b.e  | -  | -                         | ++    | -     | Mort. rate cases= 16.8%;<br>Mort. rate controls=14%<br>OR=1.245, 95%CI(0.813-1.899)  | no data  |  |
| 3                       | Kim E.S., 2014  | Comments       | Prospective study                        | difficult to have the right % of remaining patients because 126 were excluded because without a follow-up | infection had community onset                                     |  | no matching and difficult to evaluate the control since 126 patients were excluded because without a follow-up | no matching and difficult to evaluate the control since 126 patients were excluded because without a follow-up |  | 30 days   |   |  |  |                           |       |       |  |  |  |
|                         |                 | Score          | +  | HCA   | 11 cases<br>257 controls  | -  | -  | ++   | +  | ++  | ++  | ++   | -  | +                         | ++    | -     | Mort. rate cases= 18.1%<br>Mort. rate controls=37.3%   | mean cases=18<br>controls=8  |  |
| Nasal swab R vs NI      | 1               | Altinbas, 2013 | Comments                                 | Prospective study   |   | patients in ICU  |  | not matched but controlled in univariate analyses  | not matched but controlled in univariate analyses for main diseases, difference only in Gastrostomy and Femoral catheter | all nasal swabs   | 1 year  |  |  |                           |       |       |  |  |  |
|                         |                 |                | Score                                    | +   | c.b.e   | 75 cases<br>117 controls   | -  | +  | +  | +   | ++  | -  | -  | -                         | ++    | ++    | a) Mort. rate cases= 64%;<br>Mort. rate controls=44.8%;<br>b) Mort. rate cases= 30%;<br>rate controls=18.8%<br>HR=1.96, 95%CI(1.01-3.78)   | no data  |  |
|                         |                 |                | Comments                                 | Prospective cohort study  | no information available  |  | elderly patients   | patients were nursing home residents   |  |   | all nasal swabs   | 2 years  | a) all cause mortality<br>b) infection related mortality   |                           |       |       |  |  |  |
|                         |                 |                | Score                                    | -   | c.b.e   | 90 cases<br>90 controls  | -  | +  | ++   | +   | ++  | -  | -  | -                         | ++    | c.b.e | -  | Mort. rate cases= 12.2%<br>Mort. rate controls=15.6%   | mean(SD) cases=5.27<br>controls=5.9±8.8                              |
| 4                       | Moore, 2014     | Score          | ++                                       | c.b.e   | 28 cases<br>56 controls   | -  | ++   | ++   | -  | ++  | ++  | +  | -  | ++                        | ++    | -     | a) Mort. rate cases= 17%<br>Mort. rate controls=7%<br>b) Mort. rate cases= 3.6%<br>Mort. rate controls=0%  | no data  |  |
|                         |                 | Comments       | Matched case-control study               | no information available  |   | patients prior renal transplant  |  | not matched but controlled in univariate analyses for Charlson index, some other disease were different        |  | all nasal swabs   | 5 years   | a) all-cause mortality<br>b) infection related mortality |  |                           |       |       |  |  |  |
| Resp. Tract R vs NI     | 1               | Minejima, 2014 | Score                                    | -   | CA  | 134 cases<br>134 controls  | -  | +  | ++   | ++  | ++  | +  | -  | -                         | ++    | ++    | Mort. rate cases= 22%<br>Mort. rate controls=3%  | mean cases=10<br>controls=5  |  |
|                         |                 |                | Comments                                 | Retrospective study   | community onset, not specified if 100% CA                         | patients had non-MRSA pneumonia  | patients with pneumonia  |  | not matched but controlled in univariate analyses for gender, age was different  |   |   | 28 days  |  |                           |       |       |  |  |  |
| Resp. Tract R vs S      | 1               | Hill, 2013     | Score                                    | -   | c.b.e   | a) exact data*<br>80 cases<br>60 controls  | -  | +  | ++   | -   | ++  | ++   | -  | -                         | ++    | c.b.e | -  | Mort. rate cases= 17.5%<br>Mort. rate controls=26.4%   | in ICU mean cases=34<br>controls=35                                  |
|                         |                 |                | Comments                                 | Retrospective study   | no information available  | population estimated from graph  | trauma patients with VAP   |  | not matched but controlled in univariate analyses  |   | all Resp tract  | mortality in hospital                                    |  |                           |       |       |  |  |  |
|                         |                 |                | Score                                    | -   | CA  | 42 cases<br>52 controls  | -  | +  | +  | +   | ++  | ++   | ++   | +                         | -     | -     | c.b.e  | -  | Mort. rate cases= 12%<br>Mort. rate controls=2%                      |
| 2                       | Tosh, 2013      | Comments       | Retrospective study                      | community onset, not specified if 100% CA   |   | patients < 50 years  | patients with pneumonia  |  | not matched but controlled in univariate analyses for Charlson index   |   | mortality in hospital   |  |  |                           |       |       |  |  |  |
|                         |                 | Score          | -  | CA  | 78 cases<br>865 controls*   | -  | +  | ++   | ++   | ++  | +   | -  | -  | +                         | c.b.e | ++    | Mort. rate cases= 33.3%<br>Mort. rate controls=21.5%   | median (IQR) cases=16.5 (6-20)   |  |

|   |             |          |                                       |  |   |   |     |    |                                 |    |   |   |   |                       |                          |       |  |  |
|---|-------------|----------|---------------------------------------|--|---|---|-----|----|---------------------------------|----|---|---|---|-----------------------|--------------------------|-------|--|--|
| 3 | Jung, 2013  | Comments | Retrospective study                   | defined as "non-nosocomial pneumonia"                | * controls were patients with non-nosocomial pneumonia due to other bacteria (non-MRSA) |   |     |    | patients with pneumonia         |    | not matched but controlled in univariate analyses for gender, age was different |   |   | mortality in hospital |                          |       |  |  |
| 4 | Rello, 2013 | Score    | -                                     | HCA  | a) 15 cases<br>b) 5 cases<br>6 controls   | - | ++* | ++ | +                               | ++ | -   | - | - | -                     | c.b.e                    | c.b.e | a) Mort. rate cases=33.3%<br>Mort. rate controls=10%<br>b) Mort. rate cases=60%<br>Mort. rate controls=50% | no data  |
|   |             | Comments | Retrospective comparison of 2 cohorts | patient with HCA and ventilator associated pneumonia | a) Europe<br>b) Latin America   |   |     |    | patients in ICU, with pneumonia |    |   |   |   | mortality in ICU      | no information available |       |  |  |
| 5 | Self, 2016  | Score    | +                                     | CA   | 15 cases<br>22 controls   | - | +   | ++ | ++                              | ++ | -   | - | - | -                     | c.b.e                    | c.b.e | Mort. rate cases=13.3%<br>Mort. rate controls=9.1%   | median (IQR) cases=9 (8-13)<br>controls=6 (4-10) |
|   |             | Comments | Prospective study                     |  |   |   |     |    | patients with pneumonia         |    |   |   |   | mortality in hospital | no information available |       |  |  |

|   |               |          |                                    |  |   |   |   |    |                                |    |   |    |                    |   |                       |   |   |                              |
|---|---------------|----------|------------------------------------|--|---|---|---|----|--------------------------------|----|---|----|--------------------|---|-----------------------|---|---|------------------------------|
| 1 | Lin, 2015     | Score    | -                                  | Mix  | 38 cases<br>55 controls                               | - | - | ++ | -                              | ++ | +   | ++ | -                  | - | c.b.e                 | - | Mort. rate cases=5.3%<br>Mort. rate controls=5.5%   | no data                      |
|   |               | Comments | Retrospective clinical case-series | HCA: 0% cases,<br>18.4% controls<br>CA: 100% cases<br>81.6% controls | all patients had septic arthritis caused by S. aureus |   |   |    | patients with septic arthritis |    | not matched but controlled in univariate analyses for gender, age was different |    | all sinovial fluid |   | mortality in hospital |   |   |                              |
| 2 | Minguez, 2015 | Score    | -                                  | c.b.e  | 7 cases<br>17 controls                                | - | - | ++ | -                              | ++ | +   | -  | -                  | + | c.b.e                 | - | Mort. rate cases=57.1%<br>Mort. rate controls=17.6% | mean cases=33<br>controls=20 |
|   |               | Comments | Retrospective study                | no information available   | all patients had septic arthritis caused by S. aureus |   |   |    | patients with septic arthritis |    | not matched but controlled in univariate analyses for gender, age was different |    | all sinovial fluid |   | mortality in hospital |   |   |                              |

Sample size N refers to total number of cases and controls (no score)  
Calculation a priori: ++ if performed (e.g. based on expected prevalence or on literature data) or the study refers to large national surveys; - if not performed

Study type: ++ matched cohort or case-control studies; + prospective cohort or case-control studies; - retrospective database studies  
Infection type: HCA: health-care associated; CA: community associated; Mix: health-care and community associated together

Representativeness: Geographical: ++ if the study was conducted in an EU/EEA setting; + if the study was conducted in high-income country (ref. World Bank); - if the study was not conducted in an EU/EEA or high-income country setting  
Demographic: ++ if the study population represents all age groups; + if the study population represents selected age-specific groups (e.g. elderly, infants); - if the study population represents a selected sex category and age-specific groups  
Clinical: ++ if the study population represents the overall hospital population; + if the study population partially represents the hospital population; - if the study population represents a disease-specific population (e.g. liver transplanted patients, cancer patients, etc.)  
Exclusion/inclusion criteria: ++ if the same exclusion/inclusion criteria were adopted for both cases and controls; + if some (but not all) exclusion/inclusion criteria were adopted for both cases and controls; - if exclusion/inclusion criteria were different in cases and controls

Matchings or controlling for Underlying disease: ++ if performed for two or more criteria (e.g. comorbidity score, McCabe score, severity index, n. comorbidities, allergy, immunosuppression status, prior hospitalisation, etc.); + if performed for only one criteria; - if not performed at all  
Infectious site: ++ if performed; - if not performed  
Hospital and unit/ward: ++ if same hospital and same unit/ward; + if same hospital but different unit/ward; - if not same hospital and/or not same unit/ward  
Follow-up: ++ if ≥ 28 days; - if < 28 days  
Risk difference: Statistically significant outcome results: ++ if results and 95%CI are statistically significant; - if results and 95%CI are not statistically significant  
Case fatality and LOS refer to risk difference estimates in cases and controls (no score)

Scoring table

|        |   |
|--------|---|
| ++     | Matches completely/is completely fulfilled                                      |
| +      | Matches incompletely but sufficiently/is only partly but sufficiently fulfilled |
| -      | Does not match or matches insufficiently/is insufficiently fulfilled            |
| c.b.e. | Cannot be evaluated   |

| VRE   |                    |   |  |  |                                   |               |  |  |   |  |                |                        |   |  |   |   |  |
|---|--------------------|---|--|--|-----------------------------------|---------------|--|--|---|--|----------------|------------------------|---|--|---|---|--|
| Checklist for the evaluation of the most relevant studies for building antimicrobial resistance (AMR) outcome trees, healthcare-associated infection (HAI) attributable case fatality and attributable length-of-stay (LOS) |                    |   |  |  |                                   |               |  |  |   |  |                |                        |   |  |   |   |  |
| Nr  | Study              | Study type                                  | Sample size  |  | Representativeness                |               |  | Matching or controlling for confounders  |   |  |                |                        | Statistically significant outcome results | Risk difference  |   |   |  |
|   |                    |   | N (cases,controls)   | calculation a priori   | Geographical                      | Demographical | Clinical   | Exclusion/inclusion criteria   | Demographics  | Underlying disease   | Infection site | Hospital and unit/ward |   | Follow-up  | Case fatality   | LOS   |  |
|   | First author, year |   |  |  |                                   |               |  |  |   |  |                |                        |   |  | %; RR; OR; aHR; etc   | (days)  |  |
| BSI<br>R vs S   | 1                  | Score                                       | -  | 30 cases<br>284 controls   | -                                 | -             | ++   | ++   | ++  | -  | -              | -                      | ++  | c.b.e  | ++  | OR 2.73; 95% CI: 1.09-7.78  | no data  |
|   |                    | Comments                                    | Retrospective cohort study   |  |                                   |               |  |  |   |  |                |                        | all BSI                                   | same hospital and controlled in univariate analyses for ward | mortality in hospital   |   |  |
|   | 2                  | Score                                       | -  | 19 cases<br>8 controls   | -                                 | +             | ++   | -  | ++  | ++   | +              | -                      | ++  | c.b.e  | -   | Mort. rate cases=78.9%<br>Mort. rate controls=62.5%   | Mean (SD)<br>Cases=56.2 (28.2)<br>Controls=33.4(15.6)  |
|   |                    | Comments                                    | Retrospective cohort study   |  |                                   |               |  | patients who received hematopoietic stem cell transplantation or cytotoxic chemotherapy    | not matched but controlled in univariate analyses                     | not matched but controlled in univariate analyses for SAPS II score  |                |                        | all BSI                                   |  | post-discharge mortality  |   |  |
|   | 3                  | Score                                       | ++   | 53 cases<br>53 controls  | -                                 | +             | ++   | ++   | ++  | ++   | +              | -                      | ++  | -  | ++  | a)Mort. rate cases=52.8%<br>Mort. rate controls=26.4%<br>aOR=4.0; 95%CI(1.2-13.3)<br>b)Mort. rate cases=37.7%<br>Mort. rate controls=20.8%<br>bOR=52; 95%CI(1.4-2.0)  | After diagnosis<br>Mean (SD)<br>Cases=22.7 (1.88)<br>Controls=15.9 (1.7)   |
|   |                    | Comments                                    | Retrospective matched  |  |                                   |               |  |  | matched for age and controlled in univariate                          | matched for APACHE II score  |                |                        | all BSI                                   |  | 7 days  | a) all-cause mortality<br>b) infection related mortality  |  |
|   | 4                  | Score                                       | +  | 17 cases<br>169 controls   | -                                 | ++            | ++   | ++   | ++  | ++   | -              | -                      | +   | c.b.e  | -   | Mort. rate cases=23.5%<br>Mort. rate controls=12.4%<br>aOR=2.7; 95%CI(0.47-7.89)  | Mean (SD)<br>Cases=74.75 (46.27)<br>Controls=47.26 (37.59)   |
|   |                    | Comments                                    | Prospective case-control   |  |                                   |               |  |  |   | not matched but controlled in univariate analyses  |                |                        | all BSI                                   |  | mortality in hospital   |   |  |
|   | 5                  | Score                                       | -  | a)46 cases<br>23 controls<br>b) 78 cases<br>50 controls  | -                                 | +             | ++   | ++   | ++  | -  | -              | -                      | +   | c.b.e  | -   | a) Mort. rate cases=48%<br>Mort. rate controls=30%<br>aOR=1.74; 95%CI(0.59-6.12)<br>b) Mort. rate cases=43%<br>Mort. rate controls=36%<br>OR=1.28; 95%CI(0.47-3.51)   | Mean (SD)<br>Cases=39.7(25.5)<br>Controls=21(16.3)   |
|   |                    | Comments                                    | Retrospective cohort study   | a) main cohort (2 positive samples)<br>b) full cohort (1 positive sample)<br>all patients of cohort a) are present also in cohort b) |                                   |               |  |  |   |  |                |                        | all BSI                                   |  | mortality in hospital   | a) main cohort (2 positive samples)<br>b) full cohort (1 positive sample)<br>all patients of cohort a) are present also in cohort b)  |  |
|   | 6                  | Score                                       | c.b.e  | 150 cases<br>150 controls  | -                                 | +             | ++   | ++   | ++  | ++   | ++             | -                      | ++  | ++   | ++  | a) Mort. rate cases=52%<br>Mort. rate controls=27%<br>aOR=3.34; 95%CI(1.61-6.91)<br>b) Mort. rate cases=32%<br>Mort. rate controls=17%  | no data  |
|   |                    | Comments                                    | Multicentre case-control (both prospective and retrospective data) |  |                                   |               |  |  | not matched but controlled in univariate analyses                     | not matched but controlled in univariate analyses for main diseases, differences only in chronic renal failure |                |                        | all BSI                                   |  | 30 days   | a) all-cause mortality<br>b) infection related mortality  |  |
|   | 7                  | Score                                       | c.b.e  | 93 cases<br>101 controls   | -                                 | +             | ++   | ++   | ++  | ++   | -              | -                      | +   | c.b.e  | ++  | Mort. rate cases=45%<br>Mort. rate controls=27%<br>aOR=2.07; 95%CI(0.96-4.42)   | Mean<br>Cases=49.1 (48.3)<br>Controls=38.6 (31.2)  |
|   |                    | Comments                                    | Case-control study   |  |                                   |               |  |  | not matched but controlled in univariate analyses                     |  |                |                        | all BSI                                   |  | mortality in hospital   | only mortality rates comparison   |  |
|   | 8                  | Score                                       | -  | 21 cases<br>32 controls  | -                                 | +             | ++   | ++   | ++  | -  | ++             | -                      | +   | c.b.e  | ++  | a) Mort. rate cases=76%<br>Mort. rate controls=41%<br>b) Mort. rate cases=38%<br>Mort. rate controls=9%<br>c) Mort. rate cases=24%<br>Mort. rate controls=19%<br>d) Mort. rate cases=14%<br>Mort. rate controls=13% | Mean<br>Cases=34.8 (23.3)<br>Controls=16.7 (16.1)  |
|   |                    | Comments                                    | Retrospective comparison   |  |                                   |               |  |  |   | not matched but controlled in univariate analyses for severity of illness score                                |                |                        | all BSI                                   |  | mortality in hospital   | only a) and b)  | a) overall mortality<br>b) infection directly related mortality<br>c) infection indirectly related mortality<br>d) unrelated mortality |
|   | 9                  | Score                                       | -  | 54 cases<br>48 controls  | -                                 | +             | ++   | -  | ++  | -  | -              | -                      | ++  | c.b.e  | ++  | a) Mort. rate cases=57%<br>Mort. rate controls=35%<br>aRR=3.47(1.47-8.19)<br>b) Mort. rate cases=46%<br>Mort. rate controls=25%   | After diagnosis<br>Median<br>Cases=46<br>Controls=19   |
|   |                    | Comments                                    | Retrospective cohort study   |  |                                   |               |  | the patients are either awaiting liver transplantation or have received a liver transplant |   |  |                |                        | all BSI                                   |  | mortality in hospital   | a) all-cause mortality<br>b) infection related mortality  |  |
|   | 10                 | Score                                       | -  | 9 cases<br>92 controls   | -                                 | ++            | ++   | ++   | ++  | -  | -              | -                      | -   | c.b.e  | -   | Mort. rate cases=22%<br>Mort. rate controls=41.3%   | no data  |
|   |                    | Comments                                    | Retrospective review   |  |                                   |               | all ages included  |  |   |  |                |                        | all BSI                                   |  | not specified, but most probably mortality in hospital  |   |  |
|   | 11                 | Score                                       | +  | 147 cases<br>251 controls  | -                                 | +             | ++   | ++   | ++  | +  | -              | -                      | -   | ++   | ++  | Mort. rate cases=33%<br>Mort. rate controls=11%<br>aOR=2.1(1.14-3.88)   | Median cases=17<br>controls=3  |
| Comments  |                    | Prospective multicentre observational study |  |  |                                   |               |  | not matched but controlled in univariate analyses for gender, age is different             |   |  |                | all BSI                |   | 14 days  |   |   |  |
| 12  | Score              | -   | 46 cases<br>46 controls  | -  | +                                 | ++            | ++   | ++   | -   | -  | -              | +                      | c.b.e                                     | -  | Mort. rate cases=33%<br>Mort. rate controls=6.5%<br>aOR=3.3(0.7-15)   | no data   |  |
|   | Comments           | Retrospective case-control                  |  |  |                                   |               |  |  |   |  |                | all BSI                |   | not specified, but most probably mortality in hospital       |   |   |  |
| 13  | Score              | -   | 6 cases<br>37 controls   | -  | +                                 | ++            | ++   | ++   | -   | -  | -              | +                      | c.b.e                                     | -  | Mort. rate cases=17%<br>Mort. rate controls=27%   | no data   |  |
|   | Comments           | Retrospective case-control                  |  |  |                                   |               |  |  |   |  |                | all BSI                |   | mortality in hospital  |   |   |  |
| 14  | Score              | ++  | 116 cases<br>116 controls  | -  | +                                 | ++            | ++   | ++   | ++  | -  | -              | -                      | c.b.e                                     | ++   | Mort. rate cases=36%<br>Mort. rate controls=26%<br>aOR=1.21; 95%CI(0.52-2.79)   | Median (IQR)<br>cases=35(22.5-50.5)<br>controls=25(16-45.5)   |  |
|   | Comments           | Retrospective matched cohort study          |  |  |                                   |               |  | not matched but controlled in univariate analyses  |   |  |                | all BSI                |   | mortality in hospital  | only the comparison between the mortality rates   |   |  |
| 15  | Score              | -   | 22 cases<br>61 controls  | ++   | +                                 | ++            | -  | ++   | ++  | +  | -              | +                      | ++  | ++   | Mort. rate cases=63.6%<br>Mort. rate controls=41%<br>aHR=4.97; 95%CI(1.21-20.44)  | Median<br>Cases=42 (24-75)<br>Controls=31 (2-72)  |  |
|   | Comments           | Retrospective cohort study                  |  |  |                                   |               | patients with neutropenia  | not matched but controlled in univariate analyses  | not matched but controlled in univariate analyses for APACHE II score |  |                | all BSI                |   | 60 days  | only HR   |   |  |
| 16  | Score              | -   | 80 resistant<br>80 NI  | -  | +                                 | ++            | ++   | ++   | -   | -  | -              | ++                     | c.b.e                                     | ++   | Mort. rate resistant=37.5%<br>Mort. rate sensitive=8%<br>Mort. rate NI=2.5%   | no data   |  |
|   | Comments           | Case-case-control study                     |  |  |                                   |               |  |  |   |  |                | all BSI                |   | not specified, but most probably mortality in hospital       | in R and S higher than in NI  |   |  |
| 17  | Score              | -   | 10 cases<br>31 controls  | -  | +                                 | ++            | +  | ++   | -   | -  | NA             | ++                     | c.b.e                                     | -  | Mort. rate cases=40%<br>Mort. rate controls=39%   | mean (SD)<br>cases=28 (18)<br>controls=12 (10)  |  |
|   | Comments           | Retrospective cohort study                  |  |  |                                   |               | patients in ICU  |  |   |  |                |                        |   | mortality in hospital  |   |   |  |
| 18  | Score              | ++  | a)856 cases<br>1180 controls                                       | ++   | NA                                | ++            | ++   | ++   | NA  | NA   | -              | -                      | NA  | ++   | a)Mort. rate cases=41.5(0-66.7%)<br>b)Mort. rate cases=47.8(17-100%)<br>Mort. rate controls=19.0%<br>RR=2.38; 95%CI(2.13-2.66)<br>c) Mort. rate cases=48.9%<br>Mort. rate controls=19%<br>RR=2.57; 95%CI(2.27-2.91)<br>d) Mort. rate cases=28.7%<br>Mort. rate controls=10.9%<br>RR=2.62; 95%CI(1.84-3.73)<br>e) Mort. rate cases=39.1%<br>Mort. rate controls=21.8%<br>RR=1.79; 95%CI(1.28-1.5)<br>f) Attributable mortality = 17-46%    | Excess of total stay of VRE vs VSE= 10-46 days  |  |
|   | Comments           | Review and Meta-analyses                    | a)pooled cases (14 studies) and controls (26 studies)              |  | articles from different countries |               |  | different in different studies   | different in different studies  |  |                | all BSI                |   | b), c), d) and e)  | a) crude mortality rates of pooled cases (14 studies) and controls (26 studies)<br>b) pooled cases and controls from 13 studies<br>c) pooled cases and controls from 9 studies with higher sample size<br>d) pooled cases and controls from 5 studies with infection related mortality<br>e) studies of point d) excluded one that was producing heterogeneity<br>f) range of values from 4 studies which matched for severity of illness |   |  |
| 19  | Score              | ++  | 683 cases<br>891 controls  | -  | NA                                | ++            | ++   | ++   | NA  | ++   | -              | -                      | NA  | ++   | OR=2.52; 95%CI(1.9-3.4)   |   |  |
|   | Comments           | Review and Meta-analyses                    | pooled cases and controls from 9 studies                           |  | articles from different countries |               | 1 study neutropenic patients, 1 liver transplant patients but controlled with sensitivity analyses | different in different studies   | studies matched or controlled for severity of illness                 |  |                | all BSI                |   |  |   |   |  |
| 20  | Score              | -   | 71 cases<br>1810 controls  | -  | +                                 | ++            | ++   | ++   | -   | -  | -              | -                      | c.b.e                                     | -  | Mort. rate cases=36.6%<br>Mort. rate controls=16.4%   | no data   |  |
|   | Comments           | Surveillance study                          |  |  |                                   |               |  |  |   |  |                | all BSI                |   | not specified, but most probably mortality in hospital       |   |   |  |
| 21  | Score              | -   | 72 cases<br>188 controls   | -  | +                                 | ++            | ++   | ++   | -   | -  | -              | +                      | c.b.e                                     | c.b.e  | Mort. rate cases=45.8%<br>Mort. rate controls=33.5%   | Median (range)<br>cases= 23 (19.18-27.82)<br>controls= 12 (9.0-15.0)  |  |
|   | Comments           | Historical cohort study                     |  |  |                                   |               |  |  |   |  |                | all BSI                |   | not specified, but most probably mortality in hospital       | mortality rates were not compared and resistance was not significantly associated with mortality once severity of illness and age were taken into account   |   |  |

|                  |              |                   |                                     |   |                           |    |    |    |                     |    |   |  |   |   |                       |  |   |
|------------------|--------------|-------------------|-------------------------------------|---|---------------------------|----|----|----|---------------------|----|---|--|---|---|-----------------------|--|---|
| 22               | Stroud, 1996 | Score             | -                                   | 26 cases<br>119 controls                  | -                         | +  | ++ | ++ | ++                  | -  | -   | -  | -   | c.b.e   | c.b.e                 | Mort. rate cases=69%<br>Mort. rate controls=76%  | Overall cases+controls<br>mean(range)=81(9-583)<br>median=60                                      |
|                  |              | Comments          | Retrospective cohort study          |   |                           |    |    |    |                     |    |   | all BSI  |   | not specified, but most probably mortality in hospital                  | no information        | information extracted from available data in the article   |   |
| BSI<br>R vs NI   | 1            | Song, 2003        | Score                               | ++  | 159 cases<br>159 controls | ++ | +  | ++ | ++                  | ++ | +   | NA   | ++  | c.b.e   | ++                    | Mort. rate cases=50.3%<br>Mort. rate controls=27.7%<br>pOR=3.04; 95%CI(1.66-5.53)                      | Median<br>Cases=53<br>Controls=28   |
|                  |              |                   | Comments                            | Population based matched cohort study     |                           |    |    |    |                     |    |   | matched for APR-DRG complexity levels  |   |   | mortality in hospital |  |   |
|                  | 2            | Carmeli, 2002     | Score                               | ++  | 233 cases<br>647 controls | -  | +  | ++ | ++                  | ++ | -   | NA   | +   | c.b.e   | ++                    | RR= 12.3<br>Attributable mortality=25%   | Multiplicative effect:<br>2.06  |
|                  |              |                   | Comments                            | Matched cohort study                      | total sample              |    |    |    |                     |    |   | not matched but controlled in univariate analyses                              |   |   | mortality in hospital |  | infection site specific results   |
|                  | 3            | Edmond, 1996      | Score                               | ++  | 27 cases<br>27 controls   | -  | +  | ++ | ++                  | ++ | ++  | +  | NA  | +   | c.b.e                 | ++   | Mort. rate cases=67%<br>Mort. rate controls=30%<br>OR=2.3; 95%CI(1.2-4.1)                         |
| Comments         |              |                   | retrospective cohort study          |   |                           |    |    |    |                     |    |   |  |   | mortality in hospital   |                       |  |   |
| 4                | Edmond, 1995 | Score             | ++                                  | 11 cases<br>22 controls                   | -                         | +  | ++ | -  | ++                  | ++ | -   | NA   | ++  | c.b.e   | -                     | Mort. rate cases=73%<br>Mort. rate controls=30%  | Mean<br>Cases=74.75±46.27<br>Controls=47.26±37.59   |
|                  |              | Comments          | Pairwise matched case-control study |   |                           |    |    |    | Patients with tumor |    | not matched but controlled in univariate analyses | not matched but all patient with cancer  |   |   | mortality in hospital |  |   |
| 5                | Butler, 2010 | Score             | -                                   | a)94 cases<br>182 cases<br>20150 controls | -                         | +  | ++ | +  | ++                  | ++ | +   | NA   | +   | c.b.e   | ++                    | Mort. rate resistant= 32%<br>Mort. rate sensitive=17%<br>Mort. rate controls=4%                        | Attributable LOS<br>VSE=2.2 (1.5-2.7)<br>Attributable LOS<br>VSE=1.1 (0.9-1.4)                    |
|                  |              | Comments          | Retrospective cohort study          |   |                           |    |    |    | nor surgical units  |    |   | matched for propensity score   |   |   | mortality in hospital |  |   |
| UTI<br>R vs S    | 1            | Khair, 2013       | Score                               | +   | 74 cases<br>190 controls  | ++ | +  | ++ | ++                  | ++ | -   | -  | +   | c.b.e   | -                     | Mort. rate cases=14%<br>Mort. rate controls=7%   | after bacteremia<br>mean (range)<br>cases= 6.8(0.1-150.8)<br>controls= 5(0.2-78.2)                |
|                  |              |                   | Comments                            | Prospective cohort study                  |                           |    |    |    |                     |    |   | not matched but controlled in univariate analyses                              |   | all UTI   |                       | mortality in hospital  |   |
| UTI<br>R vs NI   | 1            | Carmeli, 2002     | Score                               | ++  | 233 cases<br>647 controls | -  | +  | ++ | ++                  | ++ | -   | NA   | +   | c.b.e   | ++                    | RR=4.28<br>Attributable to VRE=9%  | Multiplicative effect=1.75<br>Attributable=5.4 days   |
|                  |              |                   | Comments                            | Matched cohort study                      | total sample              |    |    |    |                     |    |   | not matched but controlled in univariate analyses                              |   |   | mortality in hospital |  | infection site specific results   |
| SSTs<br>R vs NI  | 1            | Carmeli, 2002     | Score                               | ++  | 233 cases<br>647 controls | -  | +  | ++ | ++                  | ++ | -   | NA   | +   | c.b.e   | -                     | RR=2.00<br>Attributable to VRE=6%  | Multiplicative effect=1.78<br>Attributable=6.2 days   |
|                  |              |                   | Comments                            | Matched cohort study                      | total sample              |    |    |    |                     |    |   | not matched but controlled in univariate analyses                              |   |   | mortality in hospital |  | infection site specific results   |
| Other<br>R vs NI | 1            | Carmeli, 2002     | Score                               | ++  | 647 controls              | -  | +  | ++ | ++                  | ++ | -   | NA   | +   | c.b.e   | ++                    | RR=3.75<br>Attributable to VRE=3%  | Multiplicative effect=1.42<br>Attributable=2.6 days   |
|                  |              |                   | Comments                            | Matched cohort study                      | total sample              |    |    |    |                     |    |   | not matched but controlled in univariate analyses                              |   |   | mortality in hospital |  | infection site specific results   |
| Mixed<br>R vs S  | 1            | Tornieporth, 1996 | Score                               | c.b.e                                     | 145 cases<br>145 controls | -  | +  | ++ | ++                  | ++ | +   | +  | ++  | c.b.e   | -                     | a)Mort. rate cases=37%<br>Mort. rate controls=19%<br>b)Mort. rate cases=58%<br>Mort. rate controls=43% | mean (range)<br>cases=64.5 (2-290)<br>controls=40.8 (2-248)<br>median<br>cases= 48<br>controls=26 |
|                  |              |                   | Comments                            | Case-control study                        |                           |    |    |    |                     |    |   | not matched but controlled in univariate analyses for gender, age is different | not matched but controlled in univariate analyses for main diseases, though there were some differences | not matched but controlled in univariate analyses by source of specimen |                       | mortality in hospital  |   |

**Sample size** N refers to total number of cases and controls (no score)  
**Calculation a priori:** ++ if performed (e.g. based on expected prevalence or on literature data) or the study refers to large national surveys; - if not performed

**Study type** ++ matched cohort or case-control studies; + prospective cohort or case-control studies; - retrospective database studies

**Representativeness** **Geographical:** ++ if the study was conducted in an EU/EEA setting; + if the study was conducted in high-income country (ref. World bank); - if the study was not conducted in an EU/EEA or high-income country setting  
**Demographical:** ++ if the study population represents all age groups; + if the study population represents selected age-specific groups (e.g. elderly, infants); - if the study population represents a selected sex category and age-specific groups  
**Clinical:** ++ if the study population represents the overall hospital population; + if the study population partially represents the hospital population; - if the study population represents a disease-specific population (e.g. liver transplanted patients, cancer patients, etc.)  
**Exclusion/inclusion criteria:** ++ if the same exclusion/inclusion criteria were adopted for both cases and controls; + if some (but not all) exclusion/inclusion criteria were adopted for both cases and controls; - if exclusion/inclusion criteria were different in cases and controls

**Matching or controlling for confounders** **Demographics:** ++ if performed for age and sex; + if performed only for age or only for sex; - if not performed at all  
**Underlying disease:** ++ if performed for two or more criteria (e.g. comorbidity score, McCabe score, severity index, n. comorbidities, allergy, immunosuppression status, prior hospitalisation etc.); + if performed for only one criteria; - if not performed at all  
**Infective site:** ++ if performed; - if not performed

**Risk difference** **Hospital and unit/ward:** ++ if same hospital and same unit/ward; + if same hospital but different unit/ward; - if not same hospital and/or not same unit/ward  
**Follow-up:** ++ if ≥ 28 days; - if < 28 days  
**Statistically significant outcome results:** ++ if results and 95%CI are statistically significant; - if results and 95%CI are not statistically significant  
**Case fatality and LOS** refer to risk difference estimates in cases and controls (no score)

|        |  |
|--------|--|
| ++     | Matches completely/fully fulfilled   |
| +      | Matches incompletely but sufficiently/only partly but sufficiently fulfilled |
| -      | Does not match or matches insufficiently/insufficiently fulfilled            |
| c.b.e. | Cannot be evaluated  |

| PRSP Checklist for the evaluation of the most relevant studies for building antimicrobial resistance (AMR) outcome trees, healthcare-associated infection (HAI) attributable case fatality and attributable length-of-stay (LOS) |                       |            |   |   |   |               |                   |   |                          |  |   |  |           |   |               |   |   |   |
|--|-----------------------|------------|---|---|---|---------------|-------------------|---|--------------------------|--|---|--|-----------|---|---------------|---|---|---|
| Nr   | Study                 | Study type | Sample size                                   |   | Representativeness                          |               |                   | Matching or controlling for confounders                     |                          |  |   |  |           | Statistically significant outcome results           |               | Risk difference   |   |   |
|  |                       |            | N (cases,controls)                            | calculation a priori                          | Geographical                                | Demographical | Clinical          | Exclusion/inclusion criteria                                | Demographics             | Underlying disease   | Infection site  | Hospital and unit/ward                     | Follow-up | OR, RR, OR, aHR, etc                                | Case fatality | LOS (days)  |   |   |
| 1  | Yu, 2003              | Score      | +   | 76 cases<br>598 controls                      | -   | NA            | ++                | ++  | ++                       | -  | -   | -  | -         | -   | -             | -   | Mort. rate case=23.7%<br>Mort. rate controls=15.1%  | no data                                   |
|  |                       | Comments   | Prospective international observational study |   |   | global        |                   |   |                          |  |   | all BSI                                    |           | >14 days  |               |   |   |   |
| 1  | Watanabe, 2000        | Score      | -   | 24 cases<br>25 controls                       | -   | +             | ++                | +   | ++                       | ++   | ++  | -  | +         | -   | -             | -   | a) Mort. rate case=0%<br>Mort. rate controls=8%<br>b) Mort. rate case=12.5%<br>Mort. rate controls=20%  | no data                                   |
|  |                       | Comments   | Retrospective comparative study               |   |   |               |                   | patients with pneumonia                                     |                          | not matched but controlled in univariate analyses  | not matched but controlled in univariate analyses                   | all resp tract inf, 1 control had BSI also |           | 7 days after treatment                              |               |   | a) infection related mortality<br>b) mortality due to complications   |   |
| 1  | Gouveia, 2011         | Score      | +   | 93 cases<br>248 total population              | -   | -             | ++                | -   | ++                       | -  | -   | -  | +         | -   | -             | -   | aHR=1.62; 95%CI (1.08-2.43)   | no data                                   |
|  |                       | Comments   | Prospective observational study               |   |   |               |                   | all ages  | patients with meningitis |  |   |  |           | mortality in hospital                               |               |   |   |   |
| 2  | Reechapichitkul, 2006 | Score      | -   | 22 cases<br>42 controls                       | -   | -             | ++                | +   | ++                       | -  | -   | -  | +         | -   | -             | -   | a) Mort. rate case=9.1%<br>Mort. rate controls=11.9%<br>b) Mort. rate case=9.1%<br>Mort. rate controls=9.5%   | Mean(SD) cases= 12 (9) controls= (17.7)   |
|  |                       | Comments   | Cross-sectional                               |   |   |               |                   | patients with CA pneumonia                                  |                          |  |   |  |           | mortality in hospital                               |               |   | a) all-cause mortality<br>b) pneumonia related mortality  |   |
| 3  | Sun, 2006             | Score      | -   | 44 cases<br>188 controls                      | -   | +             | ++                | +   | ++                       | ++   | ++  | -  | +         | -   | -             | -   | Mort. rate case=9%<br>Mort. rate controls=14%   | median (range) cases=6 (4-9.5) 6 (4-10.5) |
|  |                       | Comments   | Retrospective cohort study                    |   | cases are non susceptible                   |               |                   | patients with CA pneumonia                                  |                          | not matched but controlled in univariate analyses  | not matched but controlled in univariate analyses for main diseases |  |           | mortality in hospital                               |               |   |   |   |
| 4  | Song, 2004            | Score      | -   | 69 cases<br>105 controls                      | -   | NA            | ++                | +   | ++                       | -  | -   | -  | -         | ++  | -             | -   | Mort. rate case=16%<br>Mort. rate controls=12.4%<br>OR=1.3; 95%CI(0.5-3.4)  | no data                                   |
|  |                       | Comments   | Retrospective cohort study                    |   |   | Asia          |                   | patients with pneumonia                                     |                          |  |   |  |           | 30 days   |               |   |   |   |
| 5  | Einarsson, 1998       | Score      | -   | 36 cases<br>36 controls                       | -   | ++            | ++                | +   | ++                       | ++   | +   | -  | +         | -   | -             | -   | Mort. rate case=11%<br>Mort. rate controls=5.5%   | Mean Cases= 26.8 Controls= 11.5           |
|  |                       | Comments   | Retrospective case-control study              |   |   |               |                   | patients with pneumonia                                     |                          | not matched but controlled in univariate analyses for APACHE II score, differences in chronic diseases |   |  |           | not defined but most probably mortality in hospital |               |   |   |   |
| 6  | Sanghawan, 2003       | Score      | +   | 19 cases<br>27 controls                       | -   | -             | ++                | +   | ++                       | -  | -   | -  | +         | -   | -             | -   | Mort. rate case=36.8%<br>Mort. rate controls=18.5%  | no data                                   |
|  |                       | Comments   | Prospective study                             |   | cases were resistant and non susceptible    |               | patients>15 years | patients with pneumonia                                     |                          |  |   |  |           | not defined but most probably mortality in hospital |               |   |   |   |
| 7  | Falco, 2004           | Score      | c.b.e   | 15 cases<br>181 controls                      | -   | ++            | ++                | +   | ++                       | -  | -   | -  | +         | -   | -             | -   | a) Mort. rate case=26.7%<br>Mort. rate controls=12.7%<br>b) Mort. rate case=13.3%<br>Mort. rate controls=9.9%   | no data                                   |
|  |                       | Comments   | Retrospective and prospective study           |   |   |               |                   | patients with pneumonia                                     |                          |  |   |  |           | mortality in hospital                               |               |   | a) all-cause mortality<br>b) pneumonia related mortality  |   |
| 8  | Pallares, 1995        | Score      | +   | 47 cases<br>440 controls                      | -   | ++            | ++                | +   | ++                       | -  | -   | -  | +         | -   | -             | -   | Mort. rate case=<br>Mort. rate controls=<br>aOR=1.0; 95%CI(0.5-1.9)   | no data                                   |
|  |                       | Comments   | Prospective study                             |   |   |               |                   | patients with pneumonia                                     |                          |  |   |  |           | mortality in hospital                               |               |   | only the comparison between the mortality rates   |   |
| 9  | Ewig, 1999            | Score      | +   | 33 cases<br>52 controls                       | -   | ++            | ++                | +   | ++                       | -  | -   | -  | +         | -   | -             | -   | Mort. rate case=18%<br>Mort. rate controls=5.8%   | no specific data                          |
|  |                       | Comments   | Prospective study                             |   |   |               |                   | patients with CA pneumonia                                  |                          |  |   |  |           | mortality in hospital                               |               |   |   |   |
| 10   | Aspa, 2004            | Score      | +   | 64 cases<br>498 controls                      | -   | ++            | ++                | +   | ++                       | -  | -   | -  | -         | ++  | -             | -   | Mort. rate case=18.3%<br>Mort. rate controls=12.2%  | no data                                   |
|  |                       | Comments   | Prospective multi-centre study                |   |   |               | patients>16 years | patients with pneumonia                                     |                          |  |   |  |           | 30 days   |               |   |   |   |
| 11   | Falkin, 2000          | Score      | -   | a) 37 cases<br>b) 20 cases<br>c) 203 controls | -   | +             | ++                | +   | ++                       | -  | -   | -  | -         | ++  | -             | -   | a) OR= 1.3; 95%CI(0.5-3.7)<br>b) OR=2.3; 95%CI(0.7-7.4)   | no data                                   |
|  |                       | Comments   | Population-based surveillance study           |   | a) resistant<br>b) highly resistant, MIC=4  |               |                   | patients with CA pneumonia                                  |                          |  |   |  |           | 30 days   |               |   | a) resistant<br>b) highly resistant, MIC=4  |   |
| 12   | Tjeyeh, 2006          | Score      | +   | 10 studies                                    | -   | NA            | ++                | +   | ++                       | NA   | NA  | -  | -         | c.b.e   | ++            | -   | a) Mort. rate non susceptible=19.4%<br>Mort. rate controls=15.7%<br>b) OR non-susceptible=1.3; 95%CI(1.08-1.59)<br>OR intermediate=1.34; 95% CI(1.13-1.60)<br>OR resistant=1.29; 95% CI(1.01-1.66)<br>c) aRR non susceptible=1.29; 95%CI(1.04-1.59) | no data                                   |
|  |                       | Comments   | Review and meta-analysis                      |   | some included also non susceptible          |               |                   | patients with CA pneumonia                                  |                          |  |   |  |           | different based on the included studies             |               |   | a) pooled mortality rate<br>b) all cause mortality<br>c) combined adjusted (6 studies)  |   |
| 13   | Yigla, 1995           | Score      | +   | 7 cases<br>15 controls                        | -   | +             | ++                | +   | ++                       | ++   | ++  | -  | +         | -   | -             | -   | Mort. rate case=43%<br>Mort. rate controls=33%  | no data                                   |
|  |                       | Comments   | Prospective study                             |   |   |               |                   | patients with pneumonia                                     |                          | not matched but controlled in univariate analyses  | not matched but controlled in univariate analyses for main diseases |  |           | mortality in hospital                               |               |   |   |   |
| 14   | Pallares, 2002        | Score      | +   | 77 cases<br>300 controls                      | -   | ++            | ++                | ++  | ++                       | -  | -   | -  | +         | ++  | -             | -   | Mort. rate case=43%<br>Mort. rate controls=20.3%  | no data                                   |
|  |                       | Comments   | Prospective study                             |   | data extrapolated from the articles table 3 |               |                   | patients with nonmeringial systemic pneumococcal infections |                          |  |   |  |           | 30 days   |               | no information on the article because is focused on cephalosporin resistance, data extrapolated |   |   |
| 15   | Jehl, 2002            | Score      | -   | 49 cases<br>246 controls                      | -   | ++            | ++                | +   | ++                       | -  | -   | -  | -         | ++  | -             | -   | a) Mort. rate case=8.3%<br>Mort. rate controls=5.6%<br>b) Mort. rate case=4.2%<br>Mort. rate controls=10.4%<br>c) Mort. rate case=12.5%<br>Mort. rate controls=13.9%  | no data                                   |
|  |                       | Comments   | Prospective survey                            |   |   |               |                   | patients with pneumonia                                     |                          |  |   |  |           | a) 3 days<br>b) 30 days<br>c) total                 |               |   |   |   |

Sample size: N refers to total number of cases and controls (no score)  
Calculation a priori: ++ if performed (e.g. based on expected prevalence or on literature data) or the study refers to large national surveys; - if not performed

Study type: ++ matched cohort or case-control studies; + prospective cohort or case-control studies; - retrospective database studies

Representativeness: Geographical: ++ if the study was conducted in an EU/EEA setting; + if the study was conducted in high-income country (ref. World Bank); - if the study was not conducted in an EU/EEA or high-income country setting  
Demographical: ++ if the study population represents all age groups; + if the study population represents selected age-specific groups (e.g. elderly, infants); - if the study population represents a selected sex category and age-specific groups  
Clinical: ++ if the study population represents the overall hospital population; + if the study population partially represents the hospital population; - if the study population represents a disease-specific population (e.g. liver transplanted patients, cancer patients, etc.)  
Exclusion/inclusion criteria: ++ if the same exclusion/inclusion criteria were adopted for both cases and controls; + if some (but not all) exclusion/inclusion criteria were adopted for both cases and controls; - if exclusion/inclusion criteria were different in cases and controls

Matching or controlling for confounders: Demographics: ++ if performed for age and sex; + if performed only for age or only for sex; - if not performed at all  
Underlying disease: ++ if performed for two or more criteria (e.g. comorbidity score, McCabe score, severity index, n. comorbidities, allergy, immunosuppression status, prior hospitalisation, etc.); + if performed for only one criteria; - if not performed at all  
Infection site: ++ if performed; - if not performed

Hospital and unit/ward: ++ if same hospital and same unit/ward; + if same hospital but different unit/ward; - if not same hospital and/or not same unit/ward  
Follow-up: ++ if > 28 days; - if < 28 days

Risk difference: Statistically significant outcome results: ++ if results and 95%CI are statistically significant; + if results and 95%CI are not statistically significant  
Case fatality and LOS refer to risk difference estimates in cases and controls (no score)

Scoring table

|        |   |
|--------|---|
| ++     | Matches completely/is completely fulfilled                                      |
| +      | Matches incompletely but sufficiently/is only partly but sufficiently fulfilled |
| -      | Does not match or matches insufficiently/is insufficiently fulfilled            |
| c.b.e. | Cannot be evaluated   |

Mixed  
R vs S



## Burden of antimicrobial resistance

# Final disease outcome trees

Written by Alessandro Cassini and Diamantis Plachouras with contributions from Brecht Devleesschauwer, Daniel Lewandowski (for addressing comorbidities), Ana Hoxha, Carl Suetens, Liselotte Diaz Högberg, and Dominique Monnet

## Contents

|  |     |
|--|-----|
| List of abbreviations .....  | 171 |
| 1. Disease outcome trees – baseline syndromic models.....                                    | 172 |
| 1.1. Blood-stream infections.....  | 172 |
| 1.2. Respiratory tract infections.....   | 173 |
| 1.3. Urinary tract infections .....  | 174 |
| 1.4. Surgical site infections .....  | 175 |
| 1.5. Other site infections .....   | 175 |
| 2. <i>Klebsiella pneumoniae</i> resistant to third-generation cephalosporin infections ..... | 177 |
| 2.1. Blood-stream infections.....  | 177 |
| 2.2. Respiratory tract infections.....   | 177 |
| 2.3. Urinary tract infections .....  | 177 |
| 2.4. Surgical site and other site infections.....  | 177 |
| 3. <i>Klebsiella pneumoniae</i> resistant to carbapenem infections.....                      | 177 |
| 3.1. Blood-stream infections.....  | 177 |
| 3.2. Respiratory tract and surgical site infections .....                                    | 178 |
| 3.3. Urinary tract infections .....  | 178 |
| 3.4. Other site infections .....   | 178 |
| 4. <i>Klebsiella pneumoniae</i> resistant to colistin infections .....                       | 178 |
| 4.1. All infection sites.....  | 178 |
| 5. <i>Escherichia coli</i> resistant to third-generation cephalosporin infections            | 179 |
| 5.1. Blood-stream infections.....  | 179 |
| 5.2. Urinary tract infections .....  | 179 |
| 5.3. Surgical site, respiratory tract and other site infections.....                         | 179 |
| 6. <i>Escherichia coli</i> resistant to carbapenem infections .....                          | 179 |
| 6.1. All infection sites.....  | 179 |
| 7. <i>Escherichia coli</i> resistant to colistin infections .....                            | 180 |
| 7.1. All infection sites.....  | 180 |
| 8. Multidrug resistant <i>Acinetobacter</i> infections.....                                  | 180 |
| 8.1. Blood-stream infections.....  | 180 |
| 8.2. Respiratory tract infections.....   | 180 |
| 8.3. Urinary tract, surgical site and other site infections.....                             | 180 |
| 9. Carbapenem resistant <i>Acinetobacter</i> infections .....                                | 181 |
| 9.1. Blood-stream infections.....  | 181 |
| 9.2. Respiratory tract infections.....   | 181 |
| 9.3. Urinary tract, surgical site and other site infections.....                             | 181 |
| 10. Colistin resistant <i>Acinetobacter</i> infections .....                                 | 181 |
| 10.1. Blood-stream infections.....   | 181 |
| 10.2. Urinary tract infections .....   | 181 |
| 10.3. Respiratory tract, surgical site and other site infections.....                        | 181 |
| 11. Multidrug resistant <i>Pseudomonas aeruginosa</i> infections.....                        | 182 |

|  |            |
|--|------------|
| 11.1. Blood-stream infections.....   | 182        |
| 11.2. Respiratory tract infections.....  | 182        |
| 11.3. Urinary tract, surgical site and other site infections.....                          | 182        |
| <b>12. Carbapenem resistant <i>Pseudomonas aeruginosa</i> infections .....</b>             | <b>182</b> |
| 12.1. Blood-stream infections.....   | 182        |
| 12.2. Respiratory tract infections.....  | 183        |
| 12.3. Urinary tract, surgical site and other site infections.....                          | 183        |
| <b>13. Colistin resistant <i>Pseudomonas aeruginosa</i> infections.....</b>                | <b>183</b> |
| 13.1. All infection sites.....   | 183        |
| <b>14. Meticillin resistant <i>Staphylococcus aureus</i> infections.....</b>               | <b>183</b> |
| 14.1. Blood-stream infections.....   | 183        |
| 14.2. Respiratory tract infections.....  | 184        |
| 14.3. Urinary tract, surgical site and other site infections.....                          | 184        |
| <b>15. Vancomycin resistant <i>Enterococcus faecalis</i> and <i>faecium</i> infections</b> | <b>184</b> |
| 15.1. Blood-stream infections.....   | 184        |
| 15.2. Respiratory tract, urinary tract, surgical site and other site infections.....       | 184        |
| <b>16. Penicillin resistant <i>Streptococcus pneumoniae</i> infections .....</b>           | <b>185</b> |
| 16.1. Blood-stream infections.....   | 185        |
| 16.2. Respiratory tract, urinary tract, surgical site and other site infections.....       | 185        |
| <b>17. Macrolide and penicillin resistant <i>Streptococcus pneumoniae</i></b>              |            |
| <b>infections .....</b>  | <b>185</b> |
| 17.1. All infection sites.....   | 185        |
| <b>References.....</b>   | <b>186</b> |

## List of abbreviations

|          |   |
|----------|---|
| 3GCREC   | third-generation cephalosporin-resistant <i>E. coli</i>   |
| 3GCRKP   | third-generation cephalosporin-resistant <i>K. pneumoniae</i>   |
| AMR      | antimicrobial resistance  |
| BSI      | bloodstream infection   |
| CAI      | Community-associated infections   |
| CI       | confidence interval   |
| ColRACI  | colistin-resistant <i>Acinetobacter</i> spp.  |
| ColREC   | colistin-resistant <i>E. coli</i>   |
| ColRKP   | colistin-resistant <i>K. pneumoniae</i>   |
| ColRPA   | colistin-resistant <i>P. aeruginosa</i>   |
| CRACI    | carbapenem-resistant <i>Acinetobacter</i> spp.  |
| CREC     | carbapenem-resistant <i>E. coli</i>   |
| CRKP     | carbapenem-resistant <i>K. pneumoniae</i>   |
| CRPA     | carbapenem-resistant <i>P. aeruginosa</i>   |
| CSF      | cerebral spine fluid  |
| DALY     | disability-adjusted life years  |
| EARS-Net | European Antimicrobial Resistance Surveillance Network  |
| EEA      | European Economic Area  |
| EU       | European Union  |
| HAI      | healthcare-associated infection   |
| LOS      | length of stay  |
| MDR      | multidrug-resistant   |
| MDRACI   | multidrug-resistant <i>Acinetobacter</i> spp  |
| MDRPA    | multidrug-resistant <i>P. aeruginosa</i>  |
| MRSA     | meticillin-resistant <i>Staphylococcus aureus</i>   |
| MS       | Member State  |
| OECD     | Organisation for Economic Co-operation and Development  |
| OTH      | other infection site including digestive tract infections, skin and soft tissue infections (SSTI), eye, ear, nose or mouth infections, bone and joint infections, cardiovascular infections, reproductive tract infections and other less frequent infections |
| PMRSP    | penicillin- and macrolide-resistant <i>S. pneumoniae</i>  |
| PPS      | point prevalence survey of healthcare-associated infections and antimicrobial use in acute care hospitals   |
| PRSP     | penicillin-resistant <i>S. pneumoniae</i> ;   |
| RESP     | respiratory infections (including pneumonia, and low respiratory tract infection)   |
| S-BSI    | secondary BSI   |
| SP       | specified pathogens   |
| SPDAR    | specified pathogens with defined antimicrobial resistance   |
| SSI      | surgical site infection   |
| UTI      | urinary tract infection   |
| VRE      | vancomycin-resistant enterococci  |

## 1. Disease outcome trees – baseline syndromic models

The systematic review of the literature on healthcare-associated infections was the main reference for the development of the baseline models (RKI, 2016). The baseline models were built starting from the models already published for the burden of HAIs (Cassini & Plachouras, 2016). Disability weights for recurrent health outcomes between the burden of HAIs and the burden of AMR studies remained unvaried, except when corrections accounting for comorbidity were addressed (see below). Disability weights were derived from the European disability weight study (Haagsma, 2015).

A summary of disease health outcome parameters (case fatality proportion [CFP] and length of stay [LOS]) are available, see Table 1.

The outcome tree for blood-stream infections (BSI) had a number of long-term sequelae that could happen at the same time. The issue of co-morbidities has been addressed in order to account for concurrent health outcomes and with the aim to estimate their related transition probabilities and disability weights.

We assumed that the health outcomes were independent. Therefore, considering that  $x$  health outcomes will result in  $2^x$  possible combinations, we estimated  $2^4=16$  possible combinations. However, considering that physical impairment is always present as a consequence of complicated BSI infection (and discarding the ones without any transition), we considered 8 possible health outcomes, see Figure 1. The probability of each of these combinations is the product of the probability of observing each individual health state. Moreover, we also took the uncertainties around the original risk of developing the long-term sequelae through a Monte Carlo simulation approach, which implied simulating four vectors of random values for each probability and then performed calculations for each quadruplet of simulated values. One important assumption was internal comorbidity: the health outcomes are assumed to be due to a single exposure (infection with BSI) and not to multiple exposures (external comorbidity). The resulting estimated transition probabilities, median, 2.5% and 97.5% intervals, for long-term sequelae following complicated BSI infection are described in Figure 1.

As far as correcting for comorbidity of disability weights is concerned, we chose to follow the multiplicative approach (Haagsma, 2011). Here again we took uncertainties into account through Monte Carlo simulations, which resulted in a median, 2.5% and 97.5% intervals included in the related health outcomes, see Figure 1. The multiplicative approach is recommended for combining disability weights of simultaneously occurring health states. The approach allows for an increase of disability when health states are combined, while preventing the total disability level to become larger than 1, which would equal to “worse than death”.

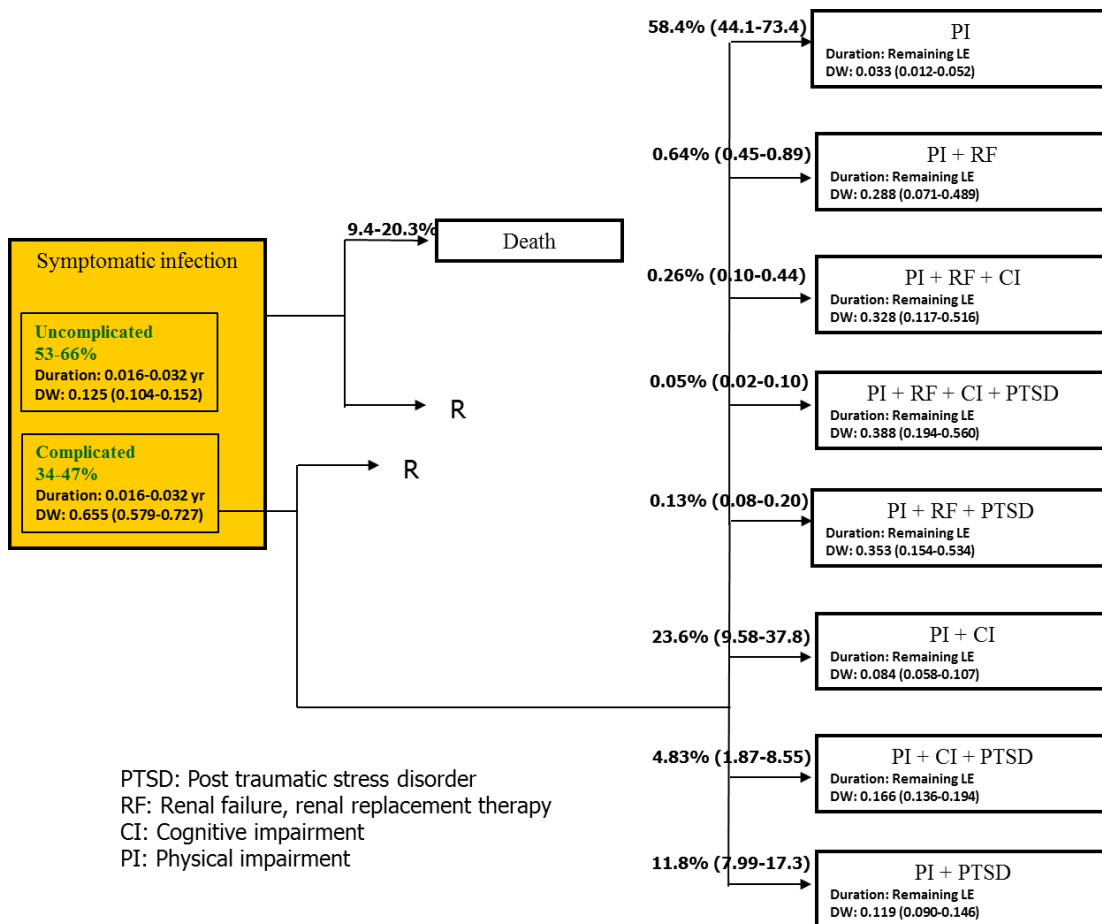
### 1.1. Blood-stream infections

The baseline attributable case fatality proportion (CFP) for blood-stream infections (BSI) was set to 7.1% (Oleachea, 2013; corresponding to mortality due to non-resistant bacterial infections as defined in the study) to 20.3% (Renaud, 2001).

The baseline attributable length of stay (LOS) was set to 5.87-11.54 days based on an extensive European study on Enterobacteriaceae and *Staphylococcus aureus* (Stewardson, 2016).

The risk of complications remained the same as for the Burden of HAIs as no specific information related to resistance patterns of the bacterial infections were available.

Figure 1. Baseline disease outcome tree for BSI



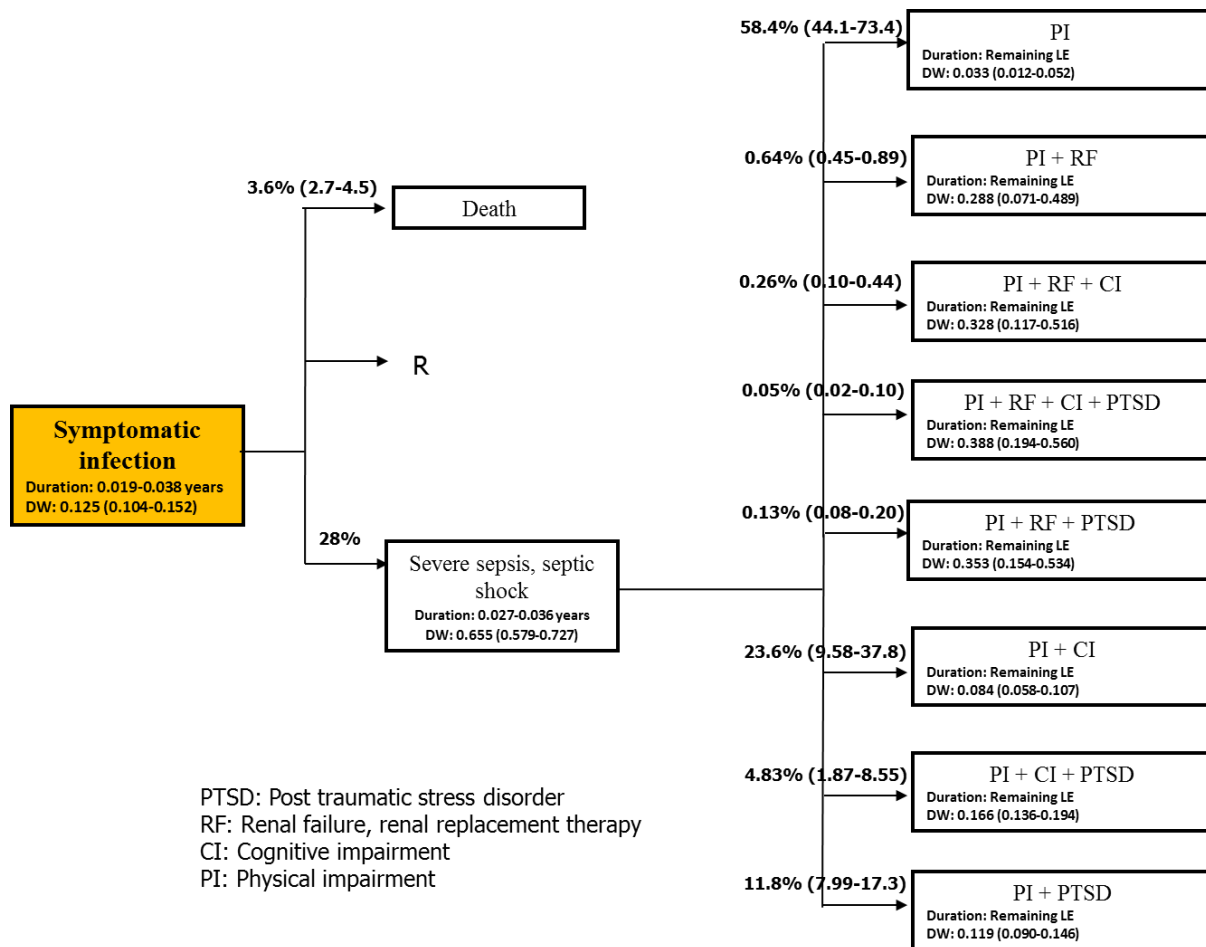
## 1.2. Respiratory tract infections

In order to estimate the CFP of respiratory infections for the baseline model, we analysed the data from the HAI-Net ICU from 2008 to 2012. After excluding all pneumonia infections developing secondary BSI and performing a propensity score matching (successful for 96.5% of pneumonia without secondary BSI), the attributable mortality was 3.6% (95% CI 2.7-4.5) and the median attributable LOS was 14 days.

The lower value of the attributable LOS remained the same as for the Burden of HAIs (7 days), as it was deemed that the propensity score matching was not ideal to estimate LOS; the higher value was set to 14 days.

The burden of HAI study considered that 39% of all patients develop severe sepsis/septic shock. Assuming that all patients with bacteraemia also have severe/septic shock, we calculated the number of patients developing secondary bacteraemia after pneumonia from the 2014 ICU-acquired infection surveillance data (ECDC, 2017). In this study 5,852 pneumonia episodes and 654 bacteraemia secondary to pneumonia were reported representing 11% of the episodes. Therefore, in order not to double-count bacteraemia we chose to subtract 11% from the 39% of risk of developing severe sepsis/septic shock. The risk of developing severe sepsis/septic shock is set to 28% and the risk of developing long-term sequelae remains the same as for the baseline BSI outcome tree described above.

Figure 2. Baseline disease outcome tree for respiratory infections

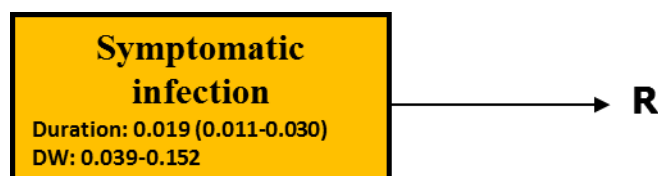


### 1.3. Urinary tract infections

It was considered that there is no risk of death due to urinary tract infections (UTIs) without development of secondary BSI (S-BSI). Therefore, the model does not include attributable CFP.

Limited evidence was available on the attributable LOS due to UTIs. Therefore, we chose to estimate the additional LOS caused by the infection from information available in the PPS 2011-2012 (ECDC, 2013). We estimated the median LN-INT, where LN is the length of stay of patients with an HAI, and INT is the length of stay before the onset of the HAI. All UTI infections were included except the resistant pathogens included in our study. Uncertainty intervals were derived by the inter-quartile range (IQR). The baseline attributable LOS was set to 7 days (4-11). Considering a high variability between cases, it was chosen to apply the 2.5% lower bound disability weight for “infectious disease, acute episode, moderate” and the 97.5% higher bound disability weight for “infectious disease, acute episode, severe”.

Figure 3. Baseline disease outcome tree for UTIs

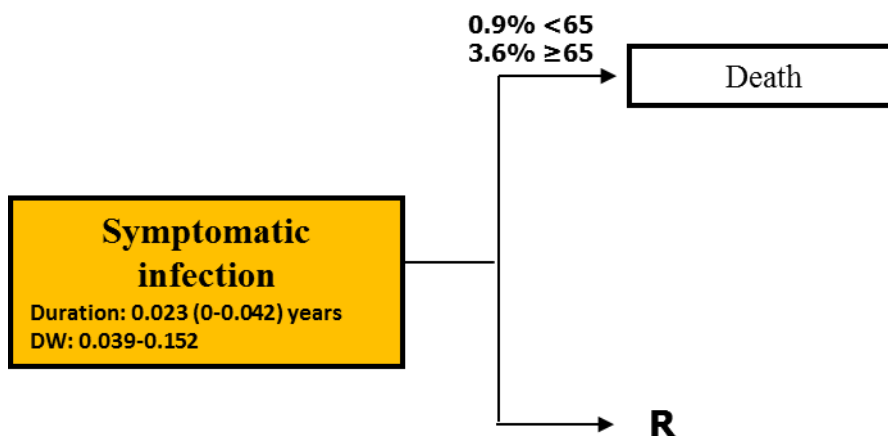


### 1.4. Surgical site infections

Attributable CFP remained the same as for the burden of HAIs study because no specific information related to bacterial infections susceptible to antibiotics were available. Moreover, death as an outcome of SSI without developing a secondary BSI was considered possible.

Attributable LOS was set to an average of 8.5 days (0-15.2 days) (Astagneau, 2001); this was lower than the attributable LOS chosen for the Burden of HAIs study because we did not exclude superficial SSI from the present burden of AMR study. Considering a high variability between cases, it was chosen to apply the 2.5% lower bound disability weight for “infectious disease, acute episode, moderate” and the 97.5% higher bound disability weight for “infectious disease, acute episode, severe”.

Figure 4. Baseline disease outcome tree for SSIs



### 1.5. Other site infections

Other site infections include digestive tract infections, skin and soft tissue infections (SSTI), eye, ear, nose or mouth infections, bone and joint infections, cardiovascular infections, reproductive tract infections and other less frequent infections.

Deaths from these infections without concomitant BSI were considered sufficiently rare. In combination with the lack of reliable data, we chose not to consider CFP in this baseline model.

Given the lack of published evidence and the variability of OTH site infections, the additional LOS caused by the infection was derived from information available in the PPS 2011-2012 (ECDC, 2013). For the OTH infection sites, we estimated the median LN-INT, where LN is the length of stay of patients with an HAI, and INT is the length of stay before the onset of the HAI. All infections defined above as OTH were included except the resistant pathogens included in our study. Uncertainty intervals were derived by the inter-quartile range (IQR). The baseline attributable LOS was set to 6 days (3-11). Considering a high variability between cases, it was chosen to apply the 2.5% lower bound disability weight for “infectious disease, acute episode, moderate” and the 97.5% higher bound disability weight for “infectious disease, acute episode, severe”

Figure 5. Baseline disease outcome tree for OTH site infections

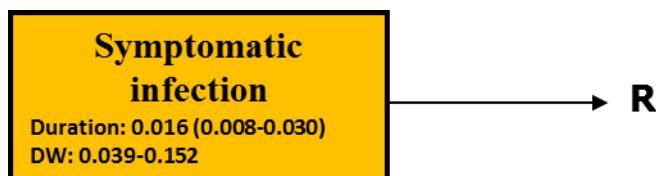




Table 1. Summary of disease health outcome parameters: case fatality proportion (CFP) and length of stay (LOS).

|                              | Baseline model | <i>Klebsiella pneumoniae</i> |            |            | <i>Escherichia coli</i> |            |            | <i>Acinetobacter</i> spp. |             |             | <i>Pseudomonas aeruginosa</i> |            |             | <i>Staphylococcus aureus</i> | <i>Enterococcus faecalis</i> and <i>E. faecium</i> | <i>Streptococcus pneumoniae</i> |           |
|------------------------------|----------------|------------------------------|------------|------------|-------------------------|------------|------------|---------------------------|-------------|-------------|-------------------------------|------------|-------------|------------------------------|--|---------------------------------|-----------|
|                              |                | 3GCRKP                       | CRKP       | CoIRKP     | 3GREC                   | CREC       | CoIREC     | MDRACI                    | CRACI       | CoIRACI     | MDRPA                         | CRPA       | CoIRPA      | MRSA                         | VRE  | PRSP                            | PMRSP     |
| <b>BSI</b>                   |                |                              |            |            |                         |            |            |                           |             |             |                               |            |             |                              |  |                                 |           |
| Case fatality proportion (%) | 7.1-20.3       | 14.4-19                      | 20-51.3    | 32-88.8    | 17.1 (9.5-26)           | 20-51.3    | 32-88.8    | 7.1-32.9                  | 7.1-34      | 7.1-34      | 7.1-35.2                      | 7.1-38.7   | 7.1-38.7    | 17.9 (14.4-21.8)             | 22.9 (21.8-23.8)                                   | 15.7-20.3                       | 15.7-20.3 |
| Duration (days)              | 5.87-11.5      | 9.28 (9.20-9.35)             | 15-35      | 15-39.1    | 6-18.5                  | 15-35      | 15-39.1    | 5.87-20.1                 | 5.87-20.1   | 5.87-20.1   | 14.87-21.5                    | 14.87-21.5 | 14.87-21.5  | 8.99-14.62                   | 6.97-18.3  | Baseline                        | Baseline  |
| <b>RESP</b>                  |                |                              |            |            |                         |            |            |                           |             |             |                               |            |             |                              |  |                                 |           |
| Case fatality proportion (%) | 3.6 (2.7-4.5)  | Baseline                     | Baseline   | Baseline   | Baseline                | Baseline   | Baseline   | Baseline                  | Baseline    | Baseline    | 2.7-9.8                       | 2.7-10.5   | 2.7-10.5    | Baseline                     | Baseline   | Baseline                        | Baseline  |
| Duration (days)              | 7-14           | 13.6-18.1                    | 13.6-18.1  | 13.6-18.1  | Baseline                | 13.6-18.1  | 13.6-18.1  | Baseline                  | Baseline    | Baseline    | 10-17                         | 15-22      | 15-22       | Baseline                     | Baseline   | Baseline                        | Baseline  |
| <b>UTI</b>                   |                |                              |            |            |                         |            |            |                           |             |             |                               |            |             |                              |  |                                 |           |
| Case fatality proportion (%) | 0              | Baseline                     | Baseline   | Baseline   | Baseline                | Baseline   | Baseline   | Baseline                  | Baseline    | Baseline    | Baseline                      | Baseline   | Baseline    | Baseline                     | Baseline   | N/A                             | N/A       |
| Duration (days)              | 7 (4-11)       | 7 (5-12)                     | 7.5 (4-14) | 7.5 (4-14) | 7 (5-12)                | 7.5 (4-14) | 7.5 (4-14) | 8 (4-11)                  | 8 (4-11)    | 8 (4-11)    | 8 (4-11)                      | 8 (4-11)   | 8 (4-11)    | Baseline                     | Baseline   | N/A                             | N/A       |
| <b>SSI</b>                   |                |                              |            |            |                         |            |            |                           |             |             |                               |            |             |                              |  |                                 |           |
| Case fatality proportion (%) | 0.9<65; 3.6>64 | Baseline                     | Baseline   | Baseline   | Baseline                | Baseline   | Baseline   | Baseline                  | Baseline    | Baseline    | Baseline                      | Baseline   | Baseline    | Baseline                     | Baseline   | N/A                             | N/A       |
| Duration (days)              | 8.5 (0-15.2)   | Baseline                     | Baseline   | Baseline   | Baseline                | Baseline   | Baseline   | Baseline                  | Baseline    | Baseline    | Baseline                      | Baseline   | Baseline    | Baseline                     | Baseline   | N/A                             | N/A       |
| <b>OTHER</b>                 |                |                              |            |            |                         |            |            |                           |             |             |                               |            |             |                              |  |                                 |           |
| Case fatality proportion (%) | 0              | Baseline                     | Baseline   | Baseline   | Baseline                | Baseline   | Baseline   | Baseline                  | Baseline    | Baseline    | Baseline                      | Baseline   | Baseline    | Baseline                     | Baseline   | 0                               | 0         |
| Duration (days)              | 6 (3-11)       | 12 (8-21)                    | 12 (6-27)  | 12 (6-27)  | 12 (8-21)               | 12 (6-27)  | 12 (6-27)  | 14.5 (9-19)               | 14.5 (9-19) | 14.5 (9-19) | 14.5 (9-19)                   | 14 (9-19)  | 14.5 (9-19) | 12 (8-19)                    | Baseline   | 5-10                            | 5-10      |

## 2. *Klebsiella pneumoniae* resistant to third-generation cephalosporin infections

### 2.1. Blood-stream infections

The review of the literature identified two studies comparing 3GCRKP infections to non-infected. A recent publication estimated an attributable CFP of 18% for MDRKP (Brady, 2017).

Attributable LOS to the 3GCRKP was set to 9.28 (9.20–9.35) (Stewardson, 2016) and the attributable CFP was set to 14.4-19% (Stewardson, 2016; Gallagher, 2014).

### 2.2. Respiratory tract infections

The review of the literature identified two studies comparing 3GCRKP infections to 3GCSKP. One study found a CFP risk difference of 8.9% and an added LOS of 9 days (Loh, 2006), whereas the second study found no added CFP and an attributable LOS of 6.6 days (Lee, 2011).

Given that the first study was done in a setting not representative of the European healthcare situation, we focused on the second study and have not added any CFP to the baseline model. We chose to add 6.6 days to the baseline model.

### 2.3. Urinary tract infections

The review of the literature identified one study focusing on solid organ transplant recipients. Moreover, this study did not exclude patients developing BSI and was excluded. Therefore, we chose to estimate the attributable LOS by applying the same methodology as the one chosen for the baseline infection model. All third-generation cephalosporin resistant Enterobacteriaceae from the PPS 2011-2012 were included and the attributable UTI LOS was set to 7 days (5-12).

### 2.4. Surgical site and other site infections

The review of the literature identified studies that did not differentiate other infection sites. Therefore, we kept the baseline models for SSIs.

The same approach for the baseline attributable LOS for OTH infection sites was used to estimate LOS. However, given the small number of observations for 3GCRKP, we chose to include all third-generation cephalosporin resistant Enterobacteriaceae from the PPS 2011-2012 in our estimation. We set the attributable LOS of OTH infections sites to 12 days (8-21).

## 3. *Klebsiella pneumoniae* resistant to carbapenem infections

### 3.1. Blood-stream infections

The review of the literature identified ten studies, three of which had non-infected patients as comparator. We excluded studies performed in specific populations, e.g. liver transplant patients (Mouloudi, 2014).

Of the two remaining studies, attributable CFP ranged from 27% to 50% and attributable LOS ranged from 3 to 35 days (Gallagher, 2014; Borer, 2009).

Seven studies compared susceptible infected patients to resistant. A met-analysis comparing CRKP to CSKP infections (Falagas, 2014) found an attributable CFP of 26-44% (this publication also reported two studies that showed no attributable mortality but these included mixed site of infection). A good-quality study (Mouloudi, 2010) found an attributable CFP compared to susceptible infections of 13%, similar to another study which found 14.7% (Hussein, 2013). The latter also found an attributable LOS of 5 days. Another retrospective cohort study found a higher attributable CFP, 31% (Ben-David, 2012), similar to a prospective observational study, 25.9% (Daikos, 2009).

When considering the baseline disease model for BSI and adding the attributable CFP, the latter ranges from 20% to 51.3%, which is similar to the studies using non-infected as comparator.

Therefore, we chose to apply a CFP of 20-51.3% to the CRKP BSI disease model.

Attributable LOS was set to 15 days (10 days from the baseline model to which we added 5 days [Hussein, 2013]) to 35 days (Gallagher, 2014).

### 3.2. Respiratory tract and surgical site infections

The literature review identified seven articles comparing CRKP infections to non-infected. We discarded those focusing on specific populations (e.g. transplant patients). Of the remaining studies, none provided specific mortality information based on site of infection. Therefore, the models baseline parameters were unvaried.

Following the review for 3GCRKP, we chose the following:

- Respiratory site infections: no added CFP. 6.6 days were added to the baseline model;
- SSI: no difference from baseline model;

### 3.3. Urinary tract infections

The review of the literature identified one study finding that CRKP UTIs have 6 added days of hospitalization compared to 3GCRKP.

We chose to estimate the attributable LOS by applying the same methodology as the one chosen for the baseline infection model. All carbapenem resistant Enterobacteriaceae from the PPS 2011-2012 were included and the attributable UTI LOS was set to 7.5 days (4-14).

### 3.4. Other site infections

The same approach for the baseline attributable LOS for OTH infection sites was used to estimate LOS. However, given the small number of observations for CRKP, we chose to include all carbapenem resistant Enterobacteriaceae in the PPS 2011-2012 in our estimation. We set the attributable LOS of OTH infections sites to 12 days (6-27).

## 4. *Klebsiella pneumoniae* resistant to colistin infections

### 4.1. All infection sites

The review of the literature identified four studies, all of which focused on mixed site of infection. The selection grid exercise clearly showed that two studies (matched case-control and prospective nested cohort) had a higher quality (Zarkotou, 2010; Rojas, 2016).

Attributable case fatality ranged from 12% (Rojas, 2016) to 37.5% (Zarkotou, 2010), and the attributable LOS ranged from no added days to 4.1 (+/- 8.5); however, it must be noted that controls were generally carbapenem resistant *K. pneumoniae* infections.

Rojas et al. show that increased attributable mortality is associated mostly with isolation in the blood. Therefore, the following decisions were made relatively to the disease models:

- Attributable CFP:
  - BSI: 12%-37.5% increase over CRKP
  - RESP: no increase from CRKP
  - SSI: no increase from CRKP
  - OTH: no increase from CRKP
- Attributable LOS
  - BSI: 0-4.1 days increase over CRKP
  - RESP: no increase from CRKP
  - SSI: no increase from CRKP
  - OTH: no increase from CRKP

## 5. *Escherichia coli* resistant to third-generation cephalosporin infections

### 5.1. Blood-stream infections

The review of the literature found one study comparing BSI resistant infections versus non-infected in 13 EU countries (de Kraker, 2011a). The univariate and multivariate analysis showed a significant impact of infections (with and without resistance) on the 30-day mortality. Death within 30 days after enrolment for resistant cases was 32% versus 6% in non-infected controls. LOS was 12 days (6-25) compared to 6 (3-16). Another EU publication (de Kraker, 2011b) estimated that 15,183 episodes of G3CREC BSIs were associated with 2,712 excess deaths, resulting in a CFP of 17.8%

The review also found 25 studies comparing BSI resistant versus susceptible infections. We excluded eight studies focusing on specific populations (e.g. haematological diseases) or where results for 3GCREC were not specifically addressed. Risk difference for CFP ranged from 2% (Van Aken, 2014) to 37.2%, although the latter was from a single-centre in 2003-2005 where the authors indicate that delayed treatment was the significant factor contributing to death (Melzer, 2007). One study with appropriate representativeness as well as a high number of cases (Martelius, 2016) found a CFP risk difference of 2.4%; another study with robust methodology undergone in the EU (Lambert, 2011) found 10% risk difference and 7 days LOS.

Of those providing ORS, three studies estimated a significant difference in mortality and three did not find a significant difference. When cumulating the information from the seventeen published studies considered above, we notice that 1,323 cases account for 276 deaths and that 10,991 controls account for 1,166 deaths. The risk difference was 10.3% (Wilson sample proportion 95% CI 8.71-11.9), which if added to the baseline values would account for a CFP of 17.4% to 30.6%.

However, we chose to combine the information from the more robust studies above and have added 2.4% and 10% to the baseline CFP of 7.1%, as well as considering the 26% from the first study. We had a similar approach for the LOS and considered 6 days (de Kraker, 2011a) compared to non-infected and 7 days (Lambert, 2011) to be added to the baseline LOS.

We applied a CFP of 17.1% (9.5-26) and a LOS of 6-18.5 days.

### 5.2. Urinary tract infections

The review of the literature found one study considering the difference in LOS between resistant infections and susceptible ones in patients with symptomatic UTIs. The study found 4.1 days LOS attributable to the resistant infection (Esteve-Palau, 2015) which if added to the baseline model would be 6.7 days.

Therefore, we chose to estimate the attributable LOS by applying the same methodology as the one chosen for the baseline infection model. All third-generation cephalosporin resistant Enterobacteriaceae from the PPS 2011-2012 were included and the attributable UTI LOS was set to 7 days (5-12).

### 5.3. Surgical site, respiratory tract and other site infections

The review of the literature did not find any specific information for other infections sites and we chose to apply the baseline models for SSI and RESP infections sites.

The same approach for the baseline attributable LOS for OTH infection sites was used to estimate LOS. However, given the small number of observations for 3GCREC, we chose to include all third-generation cephalosporin resistant Enterobacteriaceae in the PPS 2011-2012 in our estimation. We set the attributable LOS of OTH infections sites to 12 days (8-21).

## 6. *Escherichia coli* resistant to carbapenem infections

### 6.1. All infection sites

The review of the literature did not retrieve studies of sufficient quality or representativeness. Therefore, we decided to apply the same values as those for CRKP.

We chose to estimate the attributable UTI LOS by applying the same methodology as the one chosen for the baseline infection model. All carbapenem resistant Enterobacteriaceae from the PPS 2011-2012 were included and the attributable UTI LOS was set to 7.5 days (4-14).

The same approach for the baseline attributable LOS for OTH infection sites was used to estimate LOS. However, given the small number of observations for CREC, we chose to include all carbapenem resistant Enterobacteriaceae in the PPS 2011-2012 in our estimation. We set the attributable LOS of OTH infections sites to 12 days (6-27).

## 7. *Escherichia coli* resistant to colistin infections

### 7.1. All infection sites

The review of the literature did not retrieve studies of sufficient quality or representativeness. Therefore, we decided to apply the same values as those for ColRKP.

## 8. Multidrug resistant *Acinetobacter* infections

### 8.1. Blood-stream infections

The review of the literature identified two studies comparing MDRACI infections to non-infected. One study was excluded because it focused on ICU neonatal population (Al Jarousha, 2009). The other study found an attributable CFP of 24.4% (Gulen, 2015).

The review also found six studies comparing MDRACI BSI to susceptible BSI. Attributable CFP ranged from 17.8% (Smolyako, 2003) to 43.7% (Anunnatsiri, 2011) and LOS from 5.5 days (Fitzpatrick, 2015) to 20.1 days (Lee, 2007).

All four studies providing ORs found a significant impact of the resistant infection compared to the susceptible ones. When aggregating the information from the six studies, we found that 424 cases accounted for 162 deaths and 305 control accounted for 38 deaths. The risk difference was 25.8% (Wilson sample proportion 95% CI 24.5-26.2), which if added to the baseline values would account for a CFP of 32.9% to 46%.

Considering a methodologically robust study (Lambert, 2011) that found no CFP difference between susceptible and ceftazidime resistant infections, we chose to apply the baseline CFP (7.1%) and added the risk difference described above (25.8%) to this baseline CFP. Therefore, we set the MDRACI CFP to 7.1% to 32.9%. For the same reason, the lower bound value for attributable LOS of the baseline model was maintained (5.87 days) and the higher value was set to 20.1 days (Lee, 2007).

### 8.2. Respiratory tract infections

The review of the literature identified three studies comparing MDRACI infections to susceptible. We excluded one study because performed in a specific population (children) (Cai, 2012). One study found no significant difference (hazard ratio) between cases and controls (Inchai, 2015) and another had a small sample size (Park, 2006).

Therefore, we chose not to change the baseline parameters.

### 8.3. Urinary tract, surgical site and other site infections

The review of the literature identified studies that did not differentiate other infection sites (mixed infection sites). Therefore, we kept the baseline models for SSIs.

We chose to estimate the attributable UTI LOS by applying the same methodology as the one chosen for the baseline infection model. All resistant *Acinetobacter* and *Pseudomonas aeruginosa* from the PPS 2011-2012 were included and the attributable UTI LOS was set to 8 days (4-11).

The same approach for the baseline attributable LOS for OTH infection sites was used to estimate LOS. However, given the small number of observations, we chose to include all resistant

*Acinetobacter* and *Pseudomonas aeruginosa* from the PPS 2011-2012 in our estimation. We set the attributable LOS of OTH infections sites to 14.5 days (9-19).

## 9. Carbapenem resistant *Acinetobacter* infections

### 9.1. Blood-stream infections

The review of the literature identified two studies comparing CRACI infections to non-infected. Both were excluded because focused on specific populations (neonates in ICU and hematopoietic transplant patients).

The review also found eight studies comparing CRACI BSI to susceptible BSI. Excluding one study for the above-mentioned reasons (Kumar, 2014), attributable CFP OR was significant only in one study (Kim, 2012). All other studies estimating an OR (five studies) predominately showed no significant difference. When aggregating the information from the seven studies, we found that 413 cases accounted for 222 deaths and 577 controls accounted for 155 deaths. The risk difference was 26.9% (Wilson sample proportion 95% CI 25.5-27.9), which if added to the baseline values would account for a CFP of 34% to 47.2%.

Given the high uncertainty of the available evidence, we chose to maintain the baseline lower CFP (7.1%) and added the risk difference described above. Therefore, we set the CRACI CFP to 7.1% to 34%.

Two studies found an attributable LOS of 10 days (Jamulitrat, 2009; Tal-Jasper, 2016), hence we chose to maintain the same LOS as the one set for MDRACI.

### 9.2. Respiratory tract infections

The review of the literature identified one study comparing to non-infected (excluded because focusing on neonates in ICU) and three comparing to susceptible infections. The latter did not test for or find a significant attributable CFP or LOS, and the baseline parameters were kept.

### 9.3. Urinary tract, surgical site and other site infections

The review of the literature identified studies that did not differentiate other infection sites (mixed infection sites). Therefore, we kept the baseline models for SSIs.

We chose to estimate the attributable UTI LOS by applying the same methodology as the one chosen for the baseline infection model. All resistant *Acinetobacter* and *Pseudomonas aeruginosa* from the PPS 2011-2012 were included and the attributable UTI LOS was set to 8 days (4-11).

The same approach for the baseline attributable LOS for OTH infection sites was used to estimate LOS. However, given the small number of observations, we chose to include all resistant *Acinetobacter* and *Pseudomonas aeruginosa* from the PPS 2011-2012 in our estimation. We set the attributable LOS of OTH infections sites to 14.5 days (9-19).

## 10. Colistin resistant *Acinetobacter* infections

### 10.1. Blood-stream infections

The review of the literature identified one study comparing ColRACI infections to susceptible infections (Wang, 2015). No differences were reported and the CRACI model was maintained.

### 10.2. Urinary tract infections

The review of the literature identified one study comparing to susceptible infections (Taneja, 2011). No differences were reported and the CRACI model was maintained.

### 10.3. Respiratory tract, surgical site and other site infections

The review of the literature did not identify any other studies. Therefore, we kept the baseline models for respiratory tract infections and SSIs.

The same approach for the baseline attributable LOS for OTH infection sites was used to estimate LOS. However, given the small number of observations, we chose to include all resistant *Acinetobacter* and *Pseudomonas aeruginosa* from the PPS 2011-2012 in our estimation. We set the attributable LOS of OTH infections sites to 14.5 days (9-19).

## 11. Multidrug resistant *Pseudomonas aeruginosa* infections

### 11.1. Blood-stream infections

The review of the literature identified nine studies comparing MDRPA infections to susceptible infection. We discarded four studies that focused on specific populations (children, transplant patients, burned patients, haematological malignancies) and one without proper information on matching. Out of the remaining studies, the attributable CFP ranged from 0% (Morata, 2012; Joo, 2011) to 28.1% (Tam, 2010) and the attributable LOS ranged from 9 (Joo, 2011) days to 10 days (Tam, 2010; Tumbarello, 2011). Only two studies provided ORs, one indicating a significant difference in mortality and the other a non-significant difference.

When aggregating the information from the four studies, we found that 234 cases accounted for 71 deaths and that the 892 controls accounted for 245 deaths. The risk difference was 2.65% (Wilson sample proportion 95% CI 0-5.79). When added to the baseline scenario, the CFP ranged from 9.75% to 23%.

We chose to add 28.1% to the baseline CFP of 7.1% and kept 7.1% as the lower bound of the range. The MDRPA disease model was set to 7.1% to 35.2%. The attributable LOS was set 14.87 days to 21.5 days.

### 11.2. Respiratory tract infections

The review of the literature identified seven studies comparing to susceptible infections. We discarded one study that focused on COPD patients (Montero, 2009) and on ICU patients only without matching (Tumbarello, 2013); of the remaining studies, the attributable CFP ranged from 0% (Pena, 2013) to 13% (Micek, 2015) and the attributable LOS ranged from 2 (Micek, 2015) days to 3 days (Yang, 2009).

We also discarded those including secondary BSI (Micek, 2015; Yang, 2009) and the remaining studies found 0%, 4.8% (Yayan, 2015) and 5.3% (Cillóniz, 2016). We added the highest value to the highest in the baseline (4.5%); the disease model CFP was set to 2.7% to 9.8%. We set the attributable LOS to 10 to 17 days.

### 11.3. Urinary tract, surgical site and other site infections

The review of the literature did not identify any other studies. Therefore, we kept the baseline models for SSIs.

We chose to estimate the attributable UTI LOS by applying the same methodology as the one chosen for the baseline infection model. All resistant *Acinetobacter* and *Pseudomonas aeruginosa* from the PPS 2011-2012 were included and the attributable UTI LOS was set to 8 days (4-11).

The same approach for the baseline attributable LOS for OTH infection sites was used to estimate LOS. However, given the small number of observations, we chose to include all resistant *Acinetobacter* and *Pseudomonas aeruginosa* from the PPS 2011-2012 in our estimation. We set the attributable LOS of OTH infections sites to 14.5 days (9-19).

## 12. Carbapenem resistant *Pseudomonas aeruginosa* infections

### 12.1. Blood-stream infections

The review of the literature identified eight studies comparing CRPA infections to susceptible ones; we excluded one study because of a low number of cases (Hattemer, 2013) and another because of limited information on matching (Dantas, 2014). The attributable CFP ranged from 0% (Tuon, 2012;

Kim, 2014) to 18.4% (Kang, 2005) the attributable LOS ranged from 0 days (Tuon, 2012; Joo, 2011) to 10 days (Suarez, 2010).

One study found a significant difference between the mortality of resistant cases compared to susceptible, and 4 studies did not find a significant difference. When aggregating the information from the seven studies (all except the one without clear matching) and found that 410 cases accounted for 143 deaths and that 1,190 controls accounted for 338 deaths. The risk difference 6.48% (Wilson sample proportion 95% CI 4.51-8.58), which if added to the baseline would average a CFP of 13.6% to 26.8%.

Given the uncertainty and variability, we chose to maintain the baseline lower bound (7.1%) and added 18.4% to the baseline higher bound. The CRPA BSI CFP was set to 7.1%-38.7% and the attributable LOS was kept the same as for the MDRPA model.

## 12.2. Respiratory tract infections

The review of the literature identified one study comparing to susceptible that found 6% risk difference (Luyt, 2014) and 8 added days over susceptible infections. Therefore, we set the CFP to 2.7%-10.5% and the LOS to 15-22 days.

## 12.3. Urinary tract, surgical site and other site infections

The review of the literature did not identify any other studies. Therefore, we kept the baseline models for SSIs.

We chose to estimate the attributable UTI LOS by applying the same methodology as the one chosen for the baseline infection model. All resistant *Acinetobacter* and *Pseudomonas aeruginosa* from the PPS 2011-2012 were included and the attributable UTI LOS was set to 8 days (4-11).

The same approach for the baseline attributable LOS for OTH infection sites was used to estimate LOS. However, given the small number of observations, we chose to include all resistant *Acinetobacter* and *Pseudomonas aeruginosa* from the PPS 2011-2012 in our estimation. We set the attributable LOS of OTH infections sites to 14.5 days (9-19).

# 13. Colistin resistant *Pseudomonas aeruginosa* infections

## 13.1. All infection sites

The review of the literature did not retrieve studies eligible with the chosen selection criteria. Therefore, we decided to apply the same values as those for CRPA.

# 14. Meticillin resistant *Staphylococcus aureus* infections

## 14.1. Blood-stream infections

The review of the literature identified a large number of studies comparing attributable mortality and attributable LOS of MRSA to MSSA and/or non-infected patients. The WHO systematic review (WHO, 2014) found a significant impact of the resistant infection compared to susceptible ones. This meta-analysis of the WHO systematic review found an attributable mortality compared to MSSA of 10.8% (7.3-14.7) and an attributable LOS of 3.12 days (1.79-4.44). Added to the 7.1% CFP of the baseline model, the attributable CFP of MRSA would be 17.9% (14.4-21.8). When adding the attributable LOS to the baseline LOS (5.87-11.5 days), we estimated an attributable LOS compared to non-infected of 8.99-14.62 days. A recent publication estimated an attributable CFP of 19.5% (Brady, 2017).

The review of the literature identified twenty studies comparing MRSA and MSSA BSI attributable mortality. When aggregating the information from fourteen studies (after excluding those focusing only on specific populations, e.g. neonatal patients, patients with cardiac implants) we found that 1,353 cases accounted for 360 deaths and 2,954 controls accounted for 467 deaths. The resulting risk difference was 10.8% (Wilson sample proportion 95% CI 9.79-11.9), validating the result of the WHO review. Within EU countries, De Kraker et al. (de Kraker, 2011b) found that in 2007, 27,711 episodes



of MRSA BSIs were associated with 5,503 excess deaths, resulting in a 19.9% CFP. Moreover, more recent studies not included in the WHO systematic review (Stewardson, 2016; Yasmin, 2016; Atmaca, 2014) found similar attributable mortality compared to non-infected (20.4%, 20.3% and 18.2%). Therefore, we chose to apply the CFP of 17.9% (14.4-21.8).

Stewardson et al. also found an attributable LOS of 12.22 to 13.33 depending on the model used. These findings are in line with the chosen attributable LOS for the MRSA model (8.99-14.62 days).

## 14.2. Respiratory tract infections

The review of the literature identified one study comparing MRSA to non-infected and five studies comparing to MSSA. However, these studies included S-BSI patients and were discarded. We chose to apply the baseline parameters to the MRSA model.

## 14.3. Urinary tract, surgical site and other site infections

The review of the literature did not identify any other studies. Therefore, we kept the baseline models for urinary tract infections, SSIs.

The same approach for the baseline attributable LOS for OTH infection sites was used to estimate LOS. The estimated attributable LOS of MRSA OTH infection sites was set to 12 days (8-19).

# 15. Vancomycin resistant *Enterococcus faecalis* and *faecium* infections

## 15.1. Blood-stream infections

The review of the literature identified five studies comparing VRE infection attributable CFP to non-infected. CFP ranged from 12.6% to 37%. Moreover, the review also identified two meta-analysis comparing VRE to VSE which found an attributable CFP of 17% (Salgado, 2003) and the other study did not provide a risk difference but also found a significant odds ratio (DiazGranados, 2005). A recent publication estimated an attributable CFP of 13.4% for vancomycin resistant *E. faecalis* and of 19.1% for vancomycin resistant *E. faecium* (Brady, 2017).

The review of the literature identified seventeen studies comparing VRE infection VSE. Attributable CFP ranged from 0% to 29%, after excluding studies focusing only in specific populations (e.g. patients with malignancy). When aggregating the information from thirteen studies, we found that 824 cases accounted for 297 deaths and 1208 controls accounted for 245 deaths. The resulting attributable CFP was 15.8% (Wilson sample proportion 95% CI 14.7-16.7), similar to the results of the meta-analysis mentioned above.

Therefore, we decided to add this result to the baseline conservative value of 7.1% and set the attributable CFP of the VRE model to 22.9% (Wilson sample proportion 95% CI 21.8-23.8).

Attributable LOS ranged from 1.1 days to 6.8 days which were added to the baseline LOS; the attributable LOS for the VRE BSI model was set to 6.97 to 18.3 days.

## 15.2. Respiratory tract, urinary tract, surgical site and other site infections

The review of the literature identified studies focusing on other infection sites but did not exclude death by S-BSI and were excluded.

The review of the literature did not identify any other studies. Therefore, we kept the baseline models for respiratory tract infections, UTIs, SSIs and OTH infection sites. For the attributable LOS of the OTH infection sites, we explored the possibility of adopting the same approach as for the baseline model but there was a limited number of observations. Therefore, we chose to adopt the baseline attributable LOS for VRE.

## 16. Penicillin resistant *Streptococcus pneumoniae* infections

### 16.1. Blood-stream infections

The review of the literature identified one study comparing PRSP BSI to susceptible BSI infections and found a mortality risk difference of 8.6% (Yu, 2003). No information on attributable LOS was available.

The review of the literature identified one study comparing PRSP respiratory to susceptible infections and found no difference in mortality (Watanabe, 2000). No information on attributable LOS was available. A recent publication estimated an attributable CFP of 16.7% (Brady, 2017).

Therefore, for BSIs we chose to add 8.6% to the lower baseline value and keep the higher value. The PRSP BSI attributable mortality was set to 15.7%-20.3% and the baseline attributable LOS was kept unvaried.

No changes on the baseline respiratory tract infection model was made.

### 16.2. Respiratory tract, urinary tract, surgical site and other site infections

The review of the literature did not retrieve studies eligible with the chosen selection criteria. Therefore, we decided to apply the same baseline values.

The only exception was the duration of OTH infection site (mainly otitis and sinusitis) to which we chose to apply 5-10 days (Mandell, 2015).

## 17. Macrolide and penicillin resistant *Streptococcus pneumoniae* infections

### 17.1. All infection sites

The review of the literature did not retrieve studies eligible with the chosen selection criteria. Therefore, we decided to apply the same values as those for PRSP.

## References

- Al Jarousha AM, El Jadba AH, Al Afifi AS, El Qouqa IA. Nosocomial multidrug-resistant *Acinetobacter baumannii* in the neonatal intensive care unit in Gaza City, Palestine. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases*. Sep 2009;13(5):623-628.
- Anunnatsiri S, Tonsawan P. Risk factors and clinical outcomes of multidrug-resistant *Acinetobacter baumannii* bacteremia at a university hospital in Thailand. *The Southeast Asian journal of tropical medicine and public health*. May 2011;42(3):693-703.
- Astagneau P, Rioux C, Golliot F, Brucker G, Group INS. Morbidity and mortality associated with surgical site infections: results from the 1997-1999 INCISO surveillance. *J Hosp Infect*. 2001 Aug;48(4):267-74.
- Atmaca O, Zarakolu P, Karahan C, Cakir B, Unal S. [Risk factors and antibiotic use in methicillin-resistant *Staphylococcus aureus* bacteremia in hospitalized patients at Hacettepe University Adult and Oncology Hospitals (2004-2011) and antimicrobial susceptibilities of the isolates: a nested case-control study]. *Mikrobiyoloji bulteni*. Oct 2014;48(4):523-537.
- Ben-David D, Kordevani R, Keller N, et al. Outcome of carbapenem resistant *Klebsiella pneumoniae* bloodstream infections. *Clinical Microbiology and Infection*. 2012;18(1):54-60.
- Borer A, Saidel-Odes L, Riesenberk K, et al. Attributable mortality rate for carbapenem-resistant *Klebsiella pneumoniae* bacteremia. *Infection control and hospital epidemiology*. 2009;30(10):972-976.
- Brady M, Oza A, Cunney R, Burns K. Attributable mortality of hospital-acquired bloodstream infections in Ireland. *J Hosp Infect*. 2017 May;96(1):35-41.
- Cai XF, Sun JM, Bao LS, Li WB. Risk factors and antibiotic resistance of pneumonia caused by multidrug resistant *Acinetobacter baumannii* in pediatric intensive care unit. *World Journal of Emergency Medicine*. 2012;3(3):202-207.
- Cassini A, Plachouras D, Eckmanns T, Abu Sin M, Blank HP, Ducomble T, et al. Burden of Six Healthcare-Associated Infections on European Population Health: Estimating Incidence-Based Disability-Adjusted Life Years through a Population Prevalence-Based Modelling Study. *PLoS Med*. 2016;13(10):e1002150. DOI: 10.1371/journal.pone.0144988 PMID: 26672751
- Cillóniz C, Gabarrús A, Ferrer M, et al. Community-Acquired Pneumonia Due to Multidrug- and Non-Multidrug-Resistant *Pseudomonas aeruginosa*. *Chest*. 2016;150(2):415-425.
- Daikos GL, Petrikkos P, Psychogiou M, et al. Prospective observational study of the impact of VIM-1 metallo-beta-lactamase on the outcome of patients with *Klebsiella pneumoniae* bloodstream infections. *Antimicrobial agents and chemotherapy*. May 2009;53(5):1868-1873.
- Dantas RC, Ferreira ML, Gontijo-Filho PP, Ribas RM. *Pseudomonas aeruginosa* bacteraemia: independent risk factors for mortality and impact of resistance on outcome. *Journal of medical microbiology*. Dec 2014;63(Pt 12):1679-1687.
- a) de Kraker MEA, Wolkewitz M, Davey PG, et al. Burden of antimicrobial resistance in European hospitals: Excess mortality and length of hospital stay associated with bloodstream infections due to *Escherichia coli* resistant to third-generation cephalosporins. *Journal of Antimicrobial Chemotherapy*. 2011;66(2):398-407.
- b) de Kraker ME, Davey PG, Grundmann H, group Bs. Mortality and hospital stay associated with resistant *Staphylococcus aureus* and *Escherichia coli* bacteremia: estimating the burden of antibiotic resistance in Europe. *PLoS Med*. Oct 2011;8(10):e1001104.
- DiazGranados CA, Zimmer SM, Klein M, Jernigan JA. Comparison of mortality associated with vancomycin-resistant and vancomycin-susceptible enterococcal bloodstream infections: a meta-analysis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Aug 1 2005;41(3):327-333.

Esteve-Palau E, Solande G, Sanchez F, et al. Clinical and economic impact of urinary tract infections caused by ESBL-producing *Escherichia coli* requiring hospitalization: A matched cohort study. *The Journal of infection*. Dec 2015;71(6):667-674.

European Centre for Disease prevention and Control. Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals. Stockholm: ECDC; 2013. <http://ecdc.europa.eu/en/publications/Publications/healthcare-associated-infections-antimicrobialuse-PPS.pdf>.

European Centre for Disease Prevention and Control. Annual Epidemiological Report 2016 – Healthcare-associated infections acquired in intensive care units. [Internet]. Stockholm: ECDC; 2016. [cited 3 July 2017]. Available from: [http://ecdc.europa.eu/en/healthtopics/HCAI\\_ICU/Pages/Annual-epidemiological-report-2016.aspx](http://ecdc.europa.eu/en/healthtopics/HCAI_ICU/Pages/Annual-epidemiological-report-2016.aspx)

European Centre for Disease Prevention and Control. Surveillance of healthcare-associated infections in intensive care units in Europe 2008–2012, including attributable mortality analyses. Stockholm: ECDC, 2017.

Falagas ME, Tansarli GS, Karageorgopoulos DE, Vardakas KZ. Deaths attributable to carbapenem-resistant Enterobacteriaceae infections. *Emerging infectious diseases*. Jul 2014;20(7):1170-1175.

Fitzpatrick MA, Ozer E, Bolon MK, Hauser AR. Influence of ACB complex genospecies on clinical outcomes in a U.S. hospital with high rates of multidrug resistance. *The Journal of infection*. Feb 2015;70(2):144-152.

Gallagher JC, Kuriakose S, Haynes K, Axelrod P. Case-case-control study of patients with carbapenem-resistant and third-generation-cephalosporin-resistant *Klebsiella pneumoniae* bloodstream infections. *Antimicrobial agents and chemotherapy*. Oct 2014;58(10):5732-5735.

Gulen TA, Guner R, Celikbilek N, Keske S, Tasyaran M. Clinical importance and cost of bacteremia caused by nosocomial multi drug resistant *Acinetobacter baumannii*. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases*. Sep 2015;38:32-35.

Haagsma JA, van Beeck EF, Polinder S, Toet H, Panneman M, Bonsel GJ. The effect of comorbidity on health-related quality of life for injury patients in the first year following injury: comparison of three comorbidity adjustment approaches. *Population Health Metrics*. 2011;9:10. doi:10.1186/1478-7954-9-10.

Haagsma JA, Maertens de Noordhout C, Polinder S, Vos T, Havelaar AH, Cassini A, et al. Assessing disability weights based on the responses of 30,660 people from four European countries. *Popul Health Metr*. 2015; 13: 1±15. doi: 10.1186/s12963-015-0042-4 PMID: 26778920.

Hattemer A, Hauser A, Diaz M, et al. Bacterial and clinical characteristics of health care- and community-acquired bloodstream infections due to *Pseudomonas aeruginosa*. *Antimicrobial agents and chemotherapy*. Aug 2013;57(8):3969-3975.

Hussein K, Raz-Pasteur A, Finkelstein R, et al. Impact of carbapenem resistance on the outcome of patients' hospital-acquired bacteraemia caused by *Klebsiella pneumoniae*. *Journal of Hospital Infection*. 2013;83(4):307-313.

Inchai J, Pothirat C, Bumroongkit C, Limsukon A, Khositsakulchai W, Liwsrisakun C. Prognostic factors associated with mortality of drug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia. *Journal of Intensive Care*. 2015;3(1).

Jamulitrat S, Arunpan P, Phainuphong P. Attributable mortality of imipenem-resistant nosocomial *Acinetobacter baumannii* bloodstream infection. *Journal of the Medical Association of Thailand = Chotmaihet thangphaet*. Mar 2009;92(3):413-419.

Joo EJ, Kang CI, Ha YE, et al. Risk factors for mortality in patients with *Pseudomonas aeruginosa* bacteremia: clinical impact of antimicrobial resistance on outcome. *Microbial drug resistance (Larchmont, N.Y.)*. Jun 2011;17(2):305-312.

- Kang CI, Kim SH, Park WB, et al. Risk factors for antimicrobial resistance and influence of resistance on mortality in patients with bloodstream infection caused by *Pseudomonas aeruginosa*. *Microbial drug resistance* (Larchmont, N.Y.). Spring 2005;11(1):68-74.
- Kim YJ, Kim SI, Hong KW, Kim YR, Park YJ, Kang MW. Risk factors for mortality in patients with carbapenem-resistant *Acinetobacter baumannii* bacteremia: impact of appropriate antimicrobial therapy. *Journal of Korean medical science*. May 2012;27(5):471-475.
- Kim YJ, Jun YH, Kim YR, et al. Risk factors for mortality in patients with *Pseudomonas aeruginosa* bacteremia; retrospective study of impact of combination antimicrobial therapy. *BMC infectious diseases*. Mar 24 2014;14:161.
- Kumar A, Randhawa VS, Nirupam N, Rai Y, Saili A. Risk factors for carbapenem-resistant *Acinetobacter baumannii* blood stream infections in a neonatal intensive care unit, Delhi, India. *Journal of infection in developing countries*. Aug 13 2014;8(8):1049-1054.
- Lambert ML, Suetens C, Savey A, et al. Clinical outcomes of health-care-associated infections and antimicrobial resistance in patients admitted to European intensive-care units: A cohort study. *The Lancet Infectious Diseases*. 2011;11(1):30-38.
- Lee NY, Lee HC, Ko NY, et al. Clinical and economic impact of multidrug resistance in nosocomial *Acinetobacter baumannii* bacteremia. *Infection control and hospital epidemiology*. Jun 2007;28(6):713-719.
- Lee JA, Kang CI, Joo EJ, et al. Epidemiology and clinical features of community-onset bacteremia caused by extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae*. *Microbial drug resistance* (Larchmont, N.Y.). Jun 2011;17(2):267-273.
- Loh LC, Nor Izran Hanim Bt Abdul S, Rosdara Masayuni Bt Mohd S, Raman S, Thayaparan T, Kumar S. Hospital Outcomes of Adult Respiratory Tract Infections with Extended-Spectrum B-Lactamase (ESBL) Producing *Klebsiella Pneumoniae*. *The Malaysian journal of medical sciences : MJMS*. Jul 2007;14(2):36-40.
- Luyt CE, Aubry A, Lu Q, et al. Imipenem, meropenem or doripenem to treat patients with *Pseudomonas aeruginosa* ventilator-associated pneumonia. *American Journal of Respiratory and Critical Care Medicine*. 2014;189.
- Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, Eighth Edition (2015) Eds: John E. Bennett, Raphael Dolin, Martin J. Blaser. ISBN: 13-978-1-4557-4801-3, Elsevier Saunders
- Martelius T, Jalava J, Karki T, Mottonen T, Ollgren J, Lyytikäinen O. Nosocomial bloodstream infections caused by *Escherichia coli* and *Klebsiella pneumoniae* resistant to third-generation cephalosporins, Finland, 1999-2013: Trends, patient characteristics and mortality. *Infectious diseases* (London, England). 2016;48(3):229-234.
- Melzer M, Petersen I. Mortality following bacteraemic infection caused by extended spectrum beta-lactamase (ESBL) producing *E. coli* compared to non-ESBL producing *E. coli*. *The Journal of infection*. Sep 2007;55(3):254-259.
- Micek ST, Wunderink RG, Kollef MH, et al. An international multicenter retrospective study of *Pseudomonas aeruginosa* nosocomial pneumonia: impact of multidrug resistance. *Critical care* (London, England). May 06 2015;19:219.
- Montero M, Dominguez M, Orozco-Levi M, Salvado M, Knobel H. Mortality of COPD patients infected with multi-resistant *Pseudomonas aeruginosa*: a case and control study. *Infection*. Feb 2009;37(1):16-19.
- Morata L, Cobos-Trigueros N, Martinez JA, et al. Influence of multidrug resistance and appropriate empirical therapy on the 30-day mortality rate of *Pseudomonas aeruginosa* bacteremia. *Antimicrobial agents and chemotherapy*. Sep 2012;56(9):4833-4837.
- Mouloudi E, Massa E, Papadopoulos S, et al. Bloodstream infections caused by carbapenemase-producing *Klebsiella pneumoniae* among intensive care unit patients after orthotopic liver

transplantation: Risk factors for infection and impact of resistance on outcomes. *Transplantation Proceedings*. 2014;46(9):3216-3218.

Mouloudi E, Protonotariou E, Zagorianou A, et al. Bloodstream infections caused by metallo-beta-lactamase/*Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* among intensive care unit patients in Greece: risk factors for infection and impact of type of resistance on outcomes. *Infection control and hospital epidemiology*. Dec 2010;31(12):1250-1256.

Olaechea PM, Palomar M, Alvarez-Lerma F, Ojal JJ, Insausti J, Lopez-Pueyo MJ, et al. Morbidity and mortality associated with primary and catheter-related bloodstream infections in critically ill patients. *Rev Esp Quimioter*. 2013 Mar;26(1):21-9. Renaud B, Brun-Buisson C, Group IC-BS. Outcomes of primary and catheter-related bacteremia. A cohort and case-control study in critically ill patients. *Am J Respir Crit Care Med*. 2001;163(7):1584-90.

Park II, Kim IK, Koo HC, et al. Clinical characteristics and prognosis of *Acinetobacter* nosocomial pneumonia between MDR and non-MDR. *Tuberculosis and Respiratory Diseases*. 2006;61(1):13-19.

Pena C, Gomez-Zorrilla S, Oriol I, et al. Impact of multidrug resistance on *Pseudomonas aeruginosa* ventilator-associated pneumonia outcome: predictors of early and crude mortality. *European journal of clinical microbiology & infectious diseases* : official publication of the European Society of Clinical Microbiology. Mar 2013;32(3):413-420.

Robert Koch Institute. Burden of healthcare associated infection (BHAi)—evidence-based and comorbidity-adjusted outcome trees for estimation of burden of disease. Berlin: RKI; 2016. [http://www.rki.de/DE/Content/Institut/OrgEinheiten/Abt3/FG37/Research\\_Report\\_BHAi.pdf?blob=publicationFile](http://www.rki.de/DE/Content/Institut/OrgEinheiten/Abt3/FG37/Research_Report_BHAi.pdf?blob=publicationFile).

Rojas LJ, Salim M, Cober E, et al. Colistin Resistance in Carbapenem-Resistant *Klebsiella pneumoniae*: Laboratory Detection and Impact on Mortality. *Clinical infectious diseases* : an official publication of the Infectious Diseases Society of America. Dec 10 2016.

Salgado CD, Farr BM. Outcomes associated with vancomycin-resistant enterococci: a meta-analysis. *Infection control and hospital epidemiology*. Sep 2003;24(9):690-698.

Smolyakov R, Borer A, Riesenber K, et al. Nosocomial multi-drug resistant *Acinetobacter baumannii* bloodstream infection: risk factors and outcome with ampicillin-sulbactam treatment. *The Journal of hospital infection*. May 2003;54(1):32-38.

Stewardson AJ, Allignol A, Beyersmann J, et al. The health and economic burden of bloodstream infections caused by antimicrobial-susceptible and non-susceptible Enterobacteriaceae and *Staphylococcus aureus* in European hospitals, 2010 and 2011: A multicentre retrospective cohort study. *Eurosurveillance*. 2016;21(33).

Suarez C, Pena C, Gavalda L, et al. Influence of carbapenem resistance on mortality and the dynamics of mortality in *Pseudomonas aeruginosa* bloodstream infection. *International journal of infectious diseases* : IJID : official publication of the International Society for Infectious Diseases. Sep 2010;14 Suppl 3:e73-78.

Tal-Jasper R, Katz DE, Amrami N, et al. Clinical and epidemiological significance of carbapenem resistance in *Acinetobacter baumannii* infections. *Antimicrobial agents and chemotherapy*. 2016;60(5):3127-3131.

Tam VH, Rogers CA, Chang KT, Weston JS, Caeiro JP, Garey KW. Impact of multidrug-resistant *Pseudomonas aeruginosa* bacteremia on patient outcomes. *Antimicrobial agents and chemotherapy*. Sep 2010;54(9):3717-3722.

Taneja N, Singh G, Singh M, Sharma M. Emergence of tigecycline & colistin resistant *Acinetobacter baumannii* in patients with complicated urinary tract infections in north India. *Indian J Med Res*. Jun 2011;133:681-684.

Tumbarello M, Repetto E, Trecarichi EM, et al. Multidrug-resistant *Pseudomonas aeruginosa* bloodstream infections: risk factors and mortality. *Epidemiology and infection*. Nov 2011;139(11):1740-1749.

- Tumbarello M, De Pascale G, Treccarichi EM, et al. Clinical outcomes of *Pseudomonas aeruginosa* pneumonia in intensive care unit patients. *Intensive care medicine*. Apr 2013;39(4):682-692.
- Tuon FF, Gortz LW, Rocha JL. Risk factors for pan-resistant *Pseudomonas aeruginosa* bacteremia and the adequacy of antibiotic therapy. *The Brazilian journal of infectious diseases : an official publication of the Brazilian Society of Infectious Diseases*. Jul-Aug 2012;16(4):351-356.
- Van Aken S, Lund N, Ahl J, Odenholt I, Tham J. Risk factors, outcome and impact of empirical antimicrobial treatment in extended-spectrum beta-lactamase-producing *Escherichia coli* bacteraemia. *Scandinavian journal of infectious diseases*. Nov 2014;46(11):753-762.
- Wang YC, Lee YT, Yang YS, et al. Risk factors and outcome for colistin-resistant *Acinetobacter nosocomialis* bacteraemia in patients without previous colistin exposure. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. Aug 2015;21(8):758-764.
- Watanabe H, Sato S, Kawakami K, et al. A comparative clinical study of pneumonia by penicillin-resistant and -sensitive *Streptococcus pneumoniae* in a community hospital. *Respirology*. Mar 2000;5(1):59-64.
- WHO. Antimicrobial resistance: global report on surveillance. France: WHO;2014.
- Yang K, Zhuo H, Guglielmo BJ, Wiener-Kronish J. Multidrug-resistant *Pseudomonas aeruginosa* ventilator-associated pneumonia: the role of endotracheal aspirate surveillance cultures. *The Annals of pharmacotherapy*. Jan 2009;43(1):28-35.
- Yayan J, Ghebremedhin B, Rasche K. Antibiotic resistance of *Pseudomonas aeruginosa* in pneumonia at a single university hospital center in Germany over a 10-Year Period. *PloS one*. 2015;10(10).
- Yasmin M, El Hage H, Obeid R, El Haddad H, Zaarour M, Khalil A. Epidemiology of bloodstream infections caused by methicillin-resistant *Staphylococcus aureus* at a tertiary care hospital in New York. *American journal of infection control*. 2016;44(1):41-46.
- Yu VL, Chiou CC, Feldman C, et al. An international prospective study of pneumococcal bacteremia: correlation with in vitro resistance, antibiotics administered, and clinical outcome. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Jul 15 2003;37(2):230-237.
- Zarkotou O, Pournaras S, Voulgari E, et al. Risk factors and outcomes associated with acquisition of colistin-resistant KPC-producing *Klebsiella pneumoniae*: a matched case-control study. *J Clin Microbiol*. Jun 2010;48(6):2271-2274.

## Burden of antimicrobial resistance

# Methodology protocol to estimate incidence

Written by Annalisa Quattrocchi and Alessandro Cassini with contributions from Carl Suetens, Liselotte Diaz Högberg, Mélanie Colomb-Cotinat, Diamantis Plachouras and Dominique Monnet





## Contents

|   |            |
|---|------------|
| List of abbreviations .....   | 194        |
| <b>1. Introduction and background information .....</b>   | <b>195</b> |
| 1.1. European Antimicrobial Resistance Surveillance Network (EARS-Net) .....  | 195        |
| 1.2. Point Prevalence Survey of healthcare-associated infections and antimicrobial use in acute care hospitals (PPS 2011-2012) .....                  | 196        |
| <b>2. Step-by-step approach to estimate AMR infections .....</b>  | <b>197</b> |
| 2.1. Selection of Specified Pathogens (SP) .....  | 197        |
| 2.2. Data modelling for estimating total SPDAR infections.....  | 198        |
| 2.2.1. Step 1: Country-coverage adjustment .....  | 198        |
| 2.2.2. Step 2: Estimation of number of other infection sites .....  | 200        |
| 2.2.3. Step 3: Adjustment for secondary BSI .....   | 200        |
| <b>3. Approach to estimate conversion factors for penicillin-resistant and combined penicillin- and macrolide-resistant <i>S. pneumoniae</i>.....</b> | <b>202</b> |
| <b>4. Limitations.....</b>  | <b>204</b> |
| <b>References.....</b>  | <b>206</b> |
| <b>Addendum 1 .....</b>   | <b>171</b> |
| <b>Addendum 2 .....</b>   | <b>172</b> |
| <b>Addendum 3 .....</b>   | <b>172</b> |
| <b>Addendum 4 .....</b>   | <b>173</b> |

## List of abbreviations

|          |   |
|----------|---|
| 3GCREC   | third-generation cephalosporin-resistant <i>E. coli</i>   |
| 3GCRKP   | third-generation cephalosporin-resistant <i>K. pneumoniae</i>   |
| AMR      | antimicrobial resistance  |
| BSI      | bloodstream infection   |
| CAI      | Community-associated infections   |
| CI       | confidence interval   |
| ColRACI  | colistin-resistant <i>Acinetobacter</i> spp.  |
| ColREC   | colistin-resistant <i>E. coli</i>   |
| ColRKP   | colistin-resistant <i>K. pneumoniae</i>   |
| ColRPA   | colistin-resistant <i>P. aeruginosa</i>   |
| CRACI    | carbapenem-resistant <i>Acinetobacter</i> spp.  |
| CREC     | carbapenem-resistant <i>E. coli</i>   |
| CRKP     | carbapenem-resistant <i>K. pneumoniae</i>   |
| CRPA     | carbapenem-resistant <i>P. aeruginosa</i>   |
| CSF      | cerebral spine fluid  |
| DALY     | disability-adjusted life years  |
| EARS-Net | European Antimicrobial Resistance Surveillance Network  |
| EEA      | European Economic Area  |
| EU       | European Union  |
| HAI      | healthcare-associated infection   |
| LOS      | length of stay  |
| MDR      | multidrug-resistant   |
| MDRACI   | multidrug-resistant <i>Acinetobacter</i> spp  |
| MDRPA    | multidrug-resistant <i>P. aeruginosa</i>  |
| MRSA     | meticillin-resistant <i>Staphylococcus aureus</i>   |
| MS       | Member State  |
| OECD     | Organisation for Economic Co-operation and Development  |
| OTH      | other infection site including digestive tract infections, skin and soft tissue infections (SSTI), eye, ear, nose or mouth infections, bone and joint infections, cardiovascular infections, reproductive tract infections and other less frequent infections |
| PMRSP    | penicillin- and macrolide-resistant <i>S. pneumoniae</i>  |
| PPS      | point prevalence survey of healthcare-associated infections and antimicrobial use in acute care hospitals   |
| PRSP     | penicillin-resistant <i>S. pneumoniae</i> ;   |
| RESP     | respiratory infections (including pneumonia, and low respiratory tract infection)   |
| S-BSI    | secondary BSI   |
| SP       | specified pathogens   |
| SPDAR    | specified pathogens with defined antimicrobial resistance   |
| SSI      | surgical site infection   |
| UTI      | urinary tract infection   |
| VRE      | vancomycin-resistant enterococci  |

## 1. Introduction and background information

The aim of this study is to estimate the incidence of infections due to selected antimicrobial resistant (AMR) bacteria for the burden of AMR project in EU/EEA countries. Further objectives of the burden of AMR project are the estimation of the attributable case fatality, attributable length of stay (LOS), disability-adjusted life years (DALYs) and economic impact of these selected AMR infections in EU/EEA Member States.

The primary data source for the estimation of the incidence of AMR infections was the European Antimicrobial Resistance Surveillance Network (EARS-Net), for the year 2015 [3]. EARS-Net notifies the number of resistant invasive infections for a selection of pathogens. EARS-Net cases were adjusted through data from the point prevalence survey of healthcare-associated infections and antimicrobial use in acute care hospitals (PPS 2011-2012) [1] in order to estimate total country-specific number of infections, i.e. the number of non-BSI infections.

This project is conducted in collaboration with the Organisation for Economic Co-operation and Development (OECD) for the estimation of the economic burden of AMR.

### a. European Antimicrobial Resistance Surveillance Network (EARS-Net)

EARS-Net is the main EU surveillance system for antimicrobial resistance, based on a network of representatives from the Member States collecting routine clinical antimicrobial susceptibility data from national AMR surveillance initiatives.

The network collects antimicrobial susceptibility data of the first blood and/or cerebrospinal fluid isolate of every patient with an invasive infection associated with one of the pathogens under surveillance. Both antimicrobial-susceptible and antimicrobial-non-susceptible isolates are reported. The objective of EARS-Net is to measure the percentage of non-susceptible or resistant bacteria by species. Assuming that all eligible invasive isolates are reported by the participating laboratories and with country-level knowledge of the denominators (country coverage), we estimated the incidence of cases. The panels of antimicrobial agent combinations under surveillance for each microorganism, as well as algorithms for isolate prioritisation and deduplication, are defined in the EARS-Net reporting protocol [4].

Cerebrospinal fluid isolates represented 0-3% of all isolates reported to EARS-Net (6% for *S. pneumoniae*); we assumed that the patients with meningitis would most likely also have a BSI and were included in our study as BSIs.

EARS-Net performs surveillance of antimicrobial susceptibility of eight bacterial pathogens commonly causing infections in humans, hereafter referred to as “specified pathogens” (SP) and listed in table 1.

**Table 1.** Specified pathogens (SP)

| Specified pathogen                                 |
|--|
| <i>Acinetobacter</i> spp.                          |
| <i>Enterococcus faecalis</i> and <i>E. faecium</i> |
| <i>Escherichia coli</i>                            |
| <i>Klebsiella pneumoniae</i>                       |
| <i>Pseudomonas aeruginosa</i>                      |
| <i>Staphylococcus aureus</i>                       |
| <i>Streptococcus pneumoniae</i>                    |

A total of 30 countries (all EU Member States, Iceland and Norway) reported AMR data for 2015 to EARS-Net. For this study, an isolate was considered resistant to an antimicrobial group when tested and interpreted as resistant (R) in accordance with the clinical breakpoint criteria used by the local laboratory. Specific rules were applied to determine MRSA and penicillin susceptibility in *S.*

*pneumoniae*, in accordance with the EARS-Net methodology. The definition of resistance on antimicrobial group level is provided in the EARS-Net protocol [4].

## **b. Point Prevalence Survey of healthcare-associated infections and antimicrobial use in acute care hospitals (PPS 2011-2012)**

The ECDC PPS was conducted in 2011–2012 in 29 EU/EEA Member States and Croatia, and included data from a total of 273,753 patients in 1,149 hospitals [1].

It represented the first EU/EEA-wide, ECDC-coordinated PPS of healthcare-associated infections (HAIs) and antimicrobial use in acute care hospitals, representing more than 510 million citizens according to 2011 Eurostat data.

PPS collects patient-based risk factors and case-based data on selected antimicrobial resistance markers depending on microorganism, if isolated, for each HAI.

Selected antimicrobial susceptibility testing data were available on the day of the survey for 85% of microorganisms reported in HAIs. The percentage of microorganisms with known antimicrobial susceptibility testing results varied between 58% and 92%.

Representativeness of the PPS data by country (based on compliance with the recommended sampling methodology of hospitals and sample size) was reported as being optimal or good in 76% of countries.

## 2. Step-by-step approach to estimate AMR infections

### a. Selection of Specified Pathogens (SP)

The number of reported isolates including age and sex information (each representing one case) were extracted from EARS-Net and, based on resistance patterns, SPs with defined antimicrobial resistance (SPDAR) were selected. SPDAR are listed in Table 2.

Pathogens included in EARS-Net are selected in consultation with the EARS-Net disease-specific coordination committee, composed by officially nominated country representatives and external experts mainly representing collaborative institutions such as EUCAST and WHO. The European public health impact of the resistant infection, as well as availability of standardised laboratory methodology for species identification and susceptibility testing (in order to ensure reliable data) are amongst the criteria considered.

Table 2. Bacteria and antibiotic resistance categories included in the study

| Bacteria   | Antibiotic resistance <sup>‡</sup>   | Acronym |
|--|--|---------|
| <i>Acinetobacter</i> spp.                          | Colistin-resistant   | CoIRACI |
|  | Carbapenem-resistant (excluding isolates also resistant to colistin)   | CRACI   |
|  | Aminoglycoside- and fluoroquinolone-resistant <sup>#</sup> (excluding isolates also resistant to colistin and/or carbapenem) | MDRACI  |
| <i>Enterococcus faecalis</i> and <i>E. faecium</i> | Vancomycin-resistant   | VRE     |
| <i>Escherichia coli</i>                            | Colistin-resistant   | CoIREC  |
|  | Carbapenem-resistant (excluding isolates also resistant to colistin)   | CREC    |
|  | Third-generation cephalosporin-resistant* (excluding isolates also resistant to colistin and/or carbapenem)                  | 3GCREC  |
| <i>Klebsiella pneumoniae</i>                       | Colistin-resistant   | CoIRKP  |
|  | Carbapenem-resistant (excluding isolates also resistant to colistin)   | CRKP    |
|  | Third-generation cephalosporin-resistant* (excluding isolates also resistant to colistin and/or carbapenem)                  | 3GCRKP  |
| <i>Pseudomonas aeruginosa</i>                      | Colistin-resistant   | CoIRPA  |
|  | Carbapenem-resistant (excluding isolates also resistant to colistin)   | CRPA    |
|  | Resistance to three or more antibiotic groups <sup>#</sup> (excluding isolates also resistant to colistin and/or carbapenem) | MDRPA   |
| <i>Staphylococcus aureus</i>                       | Meticillin-resistant   | MRSA    |
| <i>Streptococcus pneumoniae</i>                    | Penicillin-resistant (excluding isolates also resistant to macrolides)   | PRSP    |
|  | Penicillin- and macrolide-resistant (excluding isolates only resistant to penicillin)  | PMRSP   |

<sup>‡</sup> An isolate was considered resistant to an antimicrobial group when tested and interpreted as resistant (R) in accordance with the clinical breakpoint criteria used by the local laboratory

<sup>#</sup> Resistances used as a marker of multidrug resistance

\* In 2015, most of the third-generation cephalosporin-resistant *E. coli* (88.6%) and *K. pneumoniae* (85.3%) isolates reported to EARS-Net produced an extended-spectrum  $\beta$ -lactamase (ESBL) (9).

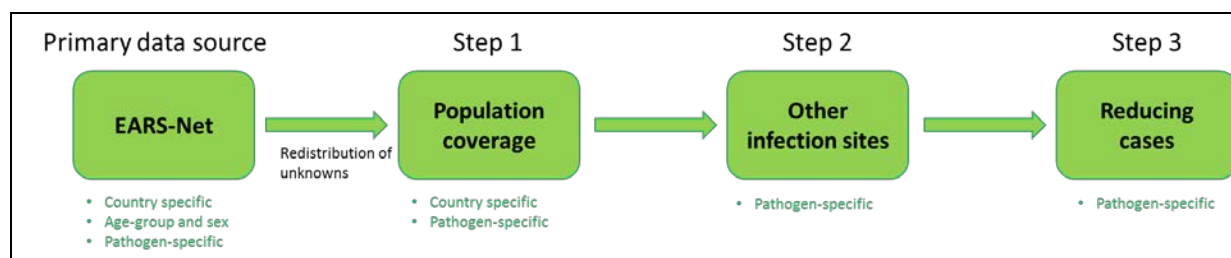
For more information on the antibiotics included in each antibiotic group, please refer to the EARS-Net protocol (5).

For each pathogen/resistance combination, unknown age-groups and sex data were re-distributed by imputation according to known cases where possible. When insufficient data was available (more than 40% of cases for an antibiotic resistance-bacterium combination with unknown age and/or sex), the cumulative EU age-group and sex distribution of the same antibiotic resistance-bacterium combination was applied for imputation. Addendum 4 provides more details of unknowns and the imputation methodology applied for each antibiotic resistance-bacterium combination in each country.

## b. Data modelling for estimating total SPDAR infections

In order to obtain all SPDAR infections a multi-step adjustment was performed. A summary description is shown in Figure 1.

**Figure 1.** Methodology for adjusting EARS-Net data in order to estimate the total number of SPDAR infections.



### i. Step 1: Country-coverage adjustment

The primary data source was EARS-Net which is based on recruited laboratories in each Member State. EARS-Net is not a population-based surveillance network, the population coverage of the laboratories contributing data to EARS-Net varies between countries and the number of cases reported does not always reflect the total number of cases in a country. During the annual EARS-Net data call, a questionnaire on the estimated population coverage is distributed to the formally designated national Focal Points (NFP) for AMR and the Operational Contact Points (OCP) for AMR. The number of designated NFPs and OCPs per country varies, but represents those working closely with the national data collection and with good insight in geographical and demographical representativeness of EARS-Net.

A limitation related to this country coverage correction approach is that case ascertainment of patients with bloodstream infections (BSIs) is strongly linked to diagnostic practices and the frequency with which blood cultures are taken. Therefore, variations in blood culture frequency or propensity to test BSIs could increase uncertainty when comparing the reported number of cases between countries and potentially underestimate the total number of cases when the blood culture frequency is low. Other limitations of the EARS-Net database considered for our study was the representativeness of the hospitals and laboratories participating: for countries reporting data from only a small number of hospitals and laboratories located in one specific geographical area, the sample may not be representative for the whole country. In addition, for countries where not all laboratories/hospitals participate in EARS-Net, the distribution of healthcare level of the sample origin might affect the patient case-mix, with the potential to both over- and underestimate the total number of cases when applying a general population coverage estimate.

Methods aiming at improving the representativeness were explored, in particular the possibility of adjusting for the frequency of use of blood cultures. EARS-Net provides some information on the number of blood culture sets per 1,000 patient days as an indicator for case ascertainment of patients with bloodstream infections. However, this information is incomplete for many countries and the denominator (i.e. 1,000 patient days) was not always homogeneously estimated across countries. In

order to provide more information on blood culturing propensity, we provided the reported number of blood culture sets per 1,000 patient days for 2015 [3] and the 2015 EU LabCap Indicator 1.32 Blood culture test rate [12], see [Addendum 4](#).

Therefore, the estimation of the country coverage for EARS-Net was mainly based on the pathogen-specific EARS-Net country population coverage, which was generally calculated based on the national ratio of admissions in reporting hospitals to total admissions in national hospitals. In an effort to partially take into account the uncertainties discussed above, designated contact points in each Member State were given the possibility of providing a range of estimated national population coverage. The estimates were expressed in percentages of population covered and the resulting multiplication factor was derived (100/population covered). Table 3 shows the estimated population country coverage per organism for each participating countries.

For each country, the total number of invasive infections due to each pathogen/resistance combination was then estimated by applying a factor based on this self-reported country coverage to the number of cases reported to EARS-Net.

**Table 3.** Estimated population country coverage per organism. All numbers are percentages.

| Country        | <i>S. pneumoniae</i> | <i>S. aureus</i> | Enterococci   | <i>E. coli</i> | <i>K. pneumoniae</i> | <i>P. aeruginosa</i> | <i>Acinetobacter</i> spp |
|----------------|----------------------|------------------|---------------|----------------|----------------------|----------------------|--------------------------|
| Austria        | 90                   | 90               | 90            | 90             | 90                   | 90                   | 90                       |
| Belgium        | 87                   | 24               | 24            | 24             | 23                   | 24                   | 8                        |
| Bulgaria       | 28-29-30             | 28-29-30         | 28-29-30      | 28-29-30       | 28-29-31             | 28-29-32             | 28-29-33                 |
| Cyprus         | 82.5-85-87.5         | 82.5-85-87.5     | 82.5-85-87.5  | 82.5-85-87.5   | 82.5-85-87.5         | 82.5-85-87.5         | 82.5-85-87.5             |
| Czech Republic | 90                   | 85               | 85            | 85             | 85                   | 85                   | 85                       |
| Germany        | 20-25-30             | 20-25-30         | 20-25-30      | 20-25-30       | 20-25-30             | 20-25-30             | 20-25-30                 |
| Denmark        | 100                  | 100              | 100           | 100            | 100                  | 100                  | 100                      |
| Estonia        | 100                  | 100              | 100           | 100            | 100                  | 100                  | 100                      |
| Greece         | NA                   | 57               | 54            | 60             | 53                   | 52                   | 60                       |
| Spain          | 27.8-31.05-34.3      | 27.8-31.05       | 27.8-31.05-34 | 27.8-31.05     | 27.8-31.05-34.3      | 27.8-31.05-34.3      | 27.8-31.05-34.3          |
| Finland        | 97-98-99             | 97-98-99         | 98-99-100     | 97-98-99       | 97-98-99             | 98-99-100            | 94-95-96                 |
| France         | 67.2                 | 12.6-18-18       | 12.6-18-18    | 12.6-18-18     | 12.6-18-18           | 12.6-18-18           | 12.6-18-18               |
| Croatia        | 85-90-95             | 85-90-95         | 85-90-95      | 85-90-95       | 85-90-95             | 85-90-95             | 85-90-95                 |
| Hungary        | 90                   | 90               | 90            | 90             | 90                   | 90                   | 90                       |
| Ireland        | 97                   | 97               | 97            | 97             | 97                   | 97                   | 97                       |
| Iceland        | 100                  | 100              | 100           | 100            | 100                  | 100                  | 100                      |
| Italy          | 10-15-20             | 10-15-20         | 10-15-20      | 10-15-20       | 10-15-20             | 10-15-20             | 10-15-20                 |
| Lithuania      | 90                   | 90               | 90            | 90             | 90                   | 90                   | 90                       |
| Luxembourg     | 100                  | 100              | 100           | 100            | 100                  | 100                  | 100                      |
| Latvia         | 90                   | 90               | 90            | 90             | 90                   | 90                   | 90                       |
| Malta          | 95                   | 95               | 95            | 95             | 95                   | 95                   | 95                       |
| Netherlands    | 65                   | 65               | 65            | 65             | 65                   | 65                   | 65                       |
| Norway         | 100                  | 100              | 100           | 100            | 100                  | 100                  | 100                      |
| Poland         | 14                   | 14               | 14            | 14             | 14                   | 14                   | 14                       |
| Portugal       | 95                   | 96.1             | 96            | 95.2           | 96.5                 | 95.3                 | 91.2                     |
| Romania        | 12-15-17             | 12-15-17         | 12-15-17      | 12-15-17       | 12-15-17             | 12-15-17             | 12-15-17                 |
| Sweden         | 75-77.5-80           | 75-77.5-80       | 75-77.5-80    | 75-77.5-80     | 75-77.5-80           | 75-77.5-80           | 60                       |
| Slovenia       | 99.1                 | 97.9             | 98.8          | 99.3           | 99.6                 | 97.9                 | 100                      |
| Slovakia       | 75                   | 75               | 75            | 75             | 75                   | 75                   | 75                       |
| United Kingdom | 21                   | 26               | 12            | 12             | 12                   | 12                   | 12                       |

ECDC is currently working with countries in standardising the sample frame and data collection methods, as well as evaluating the factors affecting the EARS-Net country coverage. These include (but not limited to): the population coverage, geographical representativeness and selection of



surveillance sites/laboratories, patient case-mix, sampling (propensity to test) and laboratory capacity and procedures (AST methods).

## ii. Step 2: Estimation of number of other infection sites

A complete picture of the burden of disease caused by infections with antibiotic-resistant bacteria requires the estimation of the number of all other types of infection. The ECDC PPS 2011-2012 focused on 29 EU/EEA countries and Croatia, and included data from a total of 273,753 patients in 1,149 hospitals. Selected antimicrobial susceptibility testing data were available for 85% of microorganisms reported in HAIs. PPS data were used to estimate the number of infections in other infection sites, except for *S. pneumoniae*.

The EU/EEA total PPS infection site incidence for each SPDAR was calculated by applying the Rhame and Sudderth formula to the prevalence data [13]. We estimated the ratio from BSI to other infection sites from the incident EU/EEA cumulative number of infections in the PPS. Particularly, we computed the number of cases for the following infections sites (according to the EU/EEA case definitions [5]):

- Bloodstream infection (BSI);
- Respiratory infection (RESP);
- Urinary tract infection (UTI);
- Surgical site infection (SSI);
- Other infection sites (OTH: excluding BSI, UTI, RESP and SSI).

The OTH group included digestive tract infections, skin and soft tissue infections (SSTIs), eye, ear, nose or mouth infections, bone and joint infections, cardiovascular infections, reproductive tract infections and other less frequent infections, caused by the selected antibiotic-resistant bacteria.

When PPS did not collect information on given SPDAR, proxies were chosen. This was the case for the following SPs:

- PPS did not collect information on colistin resistance. Therefore, carbapenem resistance of the same pathogen was used instead.
- PPS did not have enough cases of CREC; therefore, conversion factors of 3GCREC were used instead.
- PPS did not collect information on MDR *Acinetobacter* spp. Therefore, carbapenem resistant *Acinetobacter* spp. was used instead.
- PPS did not collect information on MDR *P. aeruginosa*. Therefore, carbapenem resistant *P. aeruginosa* was used instead.
- PPS did not collect information on penicillin-resistant and combined penicillin- and macrolide-resistant *S. pneumoniae*. Therefore a review of the published literature was undertaken, described in paragraph 3.

The PPS estimated ratio between BSIs and other infection sites, including 95% confidence interval (CI), were applied to the country-specific age-group and sex tables resulting from step 1. The CI of the conversion factors for each infection site were estimated by combining the CIs of the estimated infection site incidence of each SPDAR with the CIs of the incidence of BSI. The proportion of the CIs around BSI and the other infection site incidence were added and applied to the conversion factor. This approach ensures that all uncertainties are considered, but also entail very wide CIs.

For more information on infection site conversion factors for each SPDAR, please refer to [Addendum 1](#).

## iii. Step 3: Adjustment for secondary BSI

Each infection leading to secondary BSI (S-BSI) retrieved through the PPS is expected to be reported as BSI in EARS-Net. Thus, the previous adjustment might lead to double counting of the infections, resulting in overestimation of the total number of AMR infections. Therefore, the percentage of S-BSIs from each of the other infection sites (reducing factors derived from the variable 'origin of BSI' in PPS data) was deducted from infections in other sites. This deduction was applied to the number of cases for each non-BSI infection site, similarly to the example for UTIs below:

$$(UTI)_{\text{step3}} = (UTI)_{\text{step2}} - ([BSI] * x)$$

With x being the percentage of S-BSIs.

For each country and for each SPDAR, the reducing factors were applied to age-group and sex adjusted cases obtained from step 2, in order to estimate the number of all infections for each SPDAR. When the initial number of cases is low, the resulting lower uncertainty bound after Step 3 can be negative. We assumed that in those cases the lower uncertainty bound is 0.

For more information on S-BSI reducing factors for each SPDAR, please refer to [Addendum 2](#).

## Approach to estimate conversion factors for penicillin-resistant and combined penicillin- and macrolide-resistant *S. pneumoniae*

The PPS 2011-2012 did not collect information on *S. pneumoniae*. Therefore, in order to estimate a BSI/other infection site conversion factor (step 2), a review of the published literature was undertaken. The search provided a number of studies focusing on penicillin-resistant *S. pneumoniae* infection sites in European countries. However, no studies were found specifically for penicillin/macrolide combined resistance. Conversion factors for the latter infections were assumed to be the same as for penicillin-resistant infections. No studies reported *S. pneumoniae* in SSIs or in UTIs. Table 4 summarises all the results of the literature search.

ECDC report "Time to react" [6] used 2.7 as conversion between RESP/BSI.

Vardhan et al. [7] report a number of penicillin-resistant *S. pneumoniae* infections by site in adults and in children. The latter did not experience any BSI and were not considered as a separate population. Isolates from chest were considered as "Respiratory (RESP)" infections and those from the following infection sites: eye, wound/burn, ear and sinus were all considered as "other (OTH)" infections' category Hence, the conversion factors derived from this study are RESP/BSI: 8.33 and OTH/BSI: 0.54.

A textbook [8] reported a respiratory infection to BSI conversion factor of 4.

A large study in France [9] reported percentages of penicillin-resistant *S. pneumoniae* for each infection site in adults and in children, although the age group of the latter were not defined. We added the cerebral spine fluid (CSF) infections to BSIs and the middle ear fluid/sinus infections as part of the "other" category. Conversion factors for RESP/BSI was 2.97 and for other/BSI was 0.33 in adults. In children these factors change to 3.86 and 7.18, respectively. Infections resistant to erythromycin had almost the same conversion factors. However, erythromycin-resistant infections were not specified if they were also resistant to penicillin. Therefore, we decided to retain only the information on penicillin-resistant *S. pneumoniae* in adults.

Hauser et al. [10] described the number of invasive and non-invasive penicillin-resistant *S. pneumoniae* infections in Switzerland. Assuming all invasive infections as BSI (and or CSF), we estimated a conversion factor OTH/BSI of 0.28.

A study undergone in Iceland [11] found that a conversion factor for RESP/BSI of 8.07.

Notably, no reducing factors (step 3) were applied for *S. pneumoniae*.

**Table 4.** Results of the literature search

|          | Time to React (2007) [6] | Vardham (2003) [7] | Janoff (2015) [8] | Demachy (2005) [9] | Hauser (2016) [10] | Hjalmarsdottir (2014) [11] |
|----------|--------------------------|--------------------|-------------------|--------------------|--------------------|----------------------------|
| RESP/BSI | 2.7                      | 8.33               | 4                 | 2.97               | NA                 | 8.07                       |
| OTH/BSI  | NA                       | 0.54               | NA                | 0.33               | 0.28               | NA                         |

After expert opinion, it was considered that the publication from Demachy et al. [9] was the one with highest power and the following conversion factors were chosen:

| <b>Penicillin-resistant and combined penicillin- and macrolide-resistant <i>S. pneumoniae</i></b> |              |                 |                 |
|---|--------------|-----------------|-----------------|
|   | <b>Ratio</b> | <b>Lower CI</b> | <b>Upper CI</b> |
| <b>BSI</b>  | 1            | 1               | 1               |
| <b>UTI</b>  | 0            | 0               | 0               |
| <b>RESP</b>   | 2.97         | 2.7             | 8.33            |
| <b>SSI</b>  | 0            | 0               | 0               |
| <b>OTH</b>  | 0.33         | 0.28            | 0.54            |

## Limitations

A number of limitations were identified and are listed here.

Limitations related to the main data source, 2015 EARS-Net data:

- EARS-Net data relies on blood culturing and diagnostic practices, which are heterogeneous across the EU/EEA. This variability mainly concerns the frequency of testing, where under-resources countries would test less and more severe/resistant infections. A potential effect could be the under-estimation of infection numbers and the over-representation of the resistance proportion.
- EARS-Net surveillance is based on sentinel laboratories, which are assumed to be a representative sample of the country. However, in some countries participating laboratories might be concentrated in specific regions and/or in selected reference hospitals focused on high-level tertiary care. In addition, for countries where not all laboratories/hospitals participate in EARS-Net, the distribution of healthcare level of the sample origin might affect the patient case-mix, with the potential to both over- and underestimate the total number of cases when applying a general population coverage estimate.
- In order to account for blood culturing propensity, stratification of countries according to the 2015 EU LabCap Indicator 1.32 (Blood culture test rate) could be explored, see Addendum 3 of this document. However, this information is incomplete for many countries and the denominator was not always homogeneously estimated across countries.
- Countries were able to allocate a range estimates for the country coverage, in an attempt to include the resulting uncertainties in the final estimations.
- EARS-Net collects antimicrobial susceptibility data of the first blood and/or cerebrospinal fluid isolate of every patient within the year (de-duplication of data). Therefore, re-hospitalised patients would not be included; however, it is important to note that data that are not de-duplicated are more likely to overestimate resistance rates and sequelae.

Limitations related to using the PPS 2011-2012 data for converting BSI to other infections sites and to account for S-BSI:

- In order to ensure an up-to-date epidemiological picture, we chose the latest available EARS-Net reported data, from 2015. The PPS with which we derive the BSI/non-BSI conversion factors and the reduction factors accounting for S-BSI was performed in 2011 and 2012 (depending on the country). The incidence of AMR infections might have changed between these years, although the extent to which this has an impact on the BSI/non-BSI ratio was deemed to be limited.
- A number of EARS-Net infections can be considered predominately HAIs (e.g. colistin-resistant infections, *Pseudomonas* and *Acinetobacter* infections) or community-associated infections (CAIs) (e.g. *Streptococcus pneumoniae*), whereas other infections may be HAI or CAI (e.g. MRSA, Third-generation cephalosporin-resistant *E. coli*). We chose to apply the same PPS BSI/non-BSI conversion factors and the reduction factors accounting for S-BSI, irrespective of the fact of the infection is HAI or CAI. At the present stage, no published literature on the evidence for different conversion factors in CAIs was retrieved, and it was not possible to differentiate between HAI and CAI conversion factors.
- The daily national prevalence of HAI in PPS is highly variable depending on the day of the measurement. Thus, the duration of different infection types may represent a potential limitation. Long-lasting infections have a higher probability of being registered in a cross-sectional study such as the PPS than infections lasting less time and/or those treated in a timely fashion. This might affect the ratio from BSI to other types of infections, potentially resulting in an under-estimation of non-BSI infections (i.e. in particular mild infections might be under-represented). We partially account for this limitation by applying an incidence approach to the estimation of the BSI/non-BSI conversion factors and the large uncertainty

intervals resulting from the Rhame and Sudderth formula estimation of the incidence. The estimation of non-BSIs might have been affected by the case-mix of patients, which could differ between hospitals.

- The PPS study does not collect information on penicillin-resistant and combined penicillin- and macrolide-resistant *S. pneumoniae*. Therefore, conversion factors were derived from the review of the published literature. Retrieved evidence was limited and may be a source of uncertainty.

## References

1. European Centre for Disease Prevention and Control. Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals. Stockholm: ECDC; 2013. Available from: <http://ecdc.europa.eu/en/publications/Publications/healthcare-associated-infections-antimicrobial-use-PPS.pdf>
2. Cassini A, Plachouras D, Eckmanns T, Abu Sin M, Blank HP, Ducomble T, et al. Burden of Six Healthcare-Associated Infections on European Population Health: Estimating Incidence-Based Disability-Adjusted Life Years through a Population Prevalence-Based Modelling Study. *PLoS Med.* 2016 Oct;13(10):e1002150.
3. European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2015. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2017. Available from: <http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-europe-2015.pdf>
4. European Centre for Disease Prevention and Control. EARS-Net Reporting Protocol. July 2015. Stockholm: ECDC; 2015. Available from: <http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/Documents/2015-EARS-Net-reporting-protocol.pdf>
5. Brown LD, Cai TT, DasGupta A. Interval Estimation for a Binomial Proportion. *Statist. Sci.* 16 (2001), no. 2, 101--133. doi:10.1214/ss/1009213286. <http://projecteuclid.org/euclid.ss/1009213286>.
6. The bacterial challenge: time to react. A call to narrow the gap between multidrug-resistant bacteria in the EU and the development of new antibacterial agents. ECCD/EMA Joint Technical Report, 2009.
7. Vardhan MS, Allen KD. Epidemiology of penicillin-resistant pneumococci in a Merseyside Health District over a 14-year period. *J Infect.* 2003;46(1):23-9.
8. Janoff EN, Musher DM. *Streptococcus pneumoniae: Clinical syndromes.* Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, Eighth Edition. 2015 ISBN: 978-1-4557-4801-3, Elsevier, Philadelphia. Page 2319
9. Demachy MC, Vernet-Garnier V, Cottin J, Cattier B, Chardon H, Chomar M, et al. Antimicrobial resistance data on 16,756 *Streptococcus pneumoniae* isolates in 1999: A Pan-Regional Multicenter Surveillance Study in France. *Microb Drug Resist.* 2005 Winter;11(4):323-9.
10. Hauser C, Kronenberg A, Allemann A, Muhlemann K, Hilty M. Serotype/serogroup-specific antibiotic non-susceptibility of invasive and non-invasive *Streptococcus pneumoniae*, Switzerland, 2004 to 2014. *Euro surveillance.* 2016 May 26;21(21).
11. Hjalmarsdottir MA, Kristinsson KG. Epidemiology of penicillin-non-susceptible pneumococci in Iceland, 1995-2010. *J Antimicrob Chemother.* 2014 Apr;69(4):940-6.
12. European Centre for Disease Prevention and Control. European Centre for Disease Prevention and Control. EU Laboratory Capability Monitoring System (EULabCap) – Report on 2015 survey of EU/EEA country capabilities and capacities. Stockholm: ECDC; 2017. Available from: [http://ecdc.europa.eu/en/publications/Publications/EULabCap\\_report-for-2015.pdf](http://ecdc.europa.eu/en/publications/Publications/EULabCap_report-for-2015.pdf)
13. Rhame FS, Sudderth WD. Incidence and prevalence as used in the analysis of the occurrence of nosocomial infections. *Am J Epidemiol.* 1981;113(1):1-11.
- 14.

## Addendum 1

### Infection site conversion factors for each SPDAR

| <b>Colistin-/carbapenem-/multidrug-resistant <i>Acinetobacter</i> spp.*</b> |              |                 |                 |
|---|--------------|-----------------|-----------------|
|   | <b>Ratio</b> | <b>Lower CI</b> | <b>Upper CI</b> |
| <b>BSI</b>  | 1.00         | 0.76            | 1.47            |
| <b>UTI</b>  | 0.45         | 0.07            | 0.83            |
| <b>RESP</b>   | 1.23         | 0.54            | 1.93            |
| <b>SSI</b>  | 0.46         | 0.11            | 0.81            |
| <b>OTH</b>  | 0.16         | 0.01            | 0.30            |

| <b>Colistin-/carbapenem/third generation cephalosporin-resistant <i>E. coli</i>*</b> |              |                 |                 |
|--|--------------|-----------------|-----------------|
|  | <b>Ratio</b> | <b>Lower CI</b> | <b>Upper CI</b> |
| <b>BSI</b>   | 1.00         | 0.74            | 1.56            |
| <b>UTI</b>   | 4.68         | 2.10            | 7.25            |
| <b>RESP</b>  | 0.53         | 0.08            | 0.97            |
| <b>SSI</b>   | 1.24         | 0.43            | 2.05            |
| <b>OTH</b>   | 0.60         | 0.14            | 1.07            |

| <b>Vancomycin-resistant <i>E. faecalis</i> and <i>E. faecium</i></b> |              |                 |                 |
|--|--------------|-----------------|-----------------|
|  | <b>Ratio</b> | <b>Lower CI</b> | <b>Upper CI</b> |
| <b>BSI</b>   | 1.00         | 0.59            | 3.25            |
| <b>UTI</b>   | 0.75         | 0.00            | 1.87            |
| <b>RESP</b>  | 0.00         | 0.00            | 0.00            |
| <b>SSI</b>   | 1.88         | 0.00            | 4.13            |
| <b>OTH</b>   | 1.63         | 0.00            | 3.64            |



| <b>Colistin-/carbapenem-resistant <i>K. pneumoniae</i>*</b> |              |                 |                 |
|---|--------------|-----------------|-----------------|
|   | <b>Ratio</b> | <b>Lower CI</b> | <b>Upper CI</b> |
| <b>BSI</b>  | 1.00         | 0.72            | 1.62            |
| <b>UTI</b>  | 0.74         | 0.13            | 1.35            |
| <b>RESP</b>   | 0.64         | 0.07            | 1.20            |
| <b>SSI</b>  | 0.37         | 0.00            | 0.75            |
| <b>OTH</b>  | 0.68         | 0.09            | 1.27            |

| <b>Third-generation cephalosporin- resistant <i>K. pneumoniae</i></b> |              |                 |                 |
|---|--------------|-----------------|-----------------|
|   | <b>Ratio</b> | <b>Lower CI</b> | <b>Upper CI</b> |
| <b>BSI</b>  | 1.00         | 0.78            | 1.34            |
| <b>UTI</b>  | 1.52         | 0.79            | 2.29            |
| <b>RESP</b>   | 0.94         | 0.44            | 1.47            |
| <b>SSI</b>  | 0.43         | 0.16            | 0.72            |
| <b>OTH</b>  | 0.50         | 0.21            | 0.81            |

| <b>Colistin-/carbapenem-/multidrug-resistant <i>P. aeruginosa</i>*</b> |              |                 |                 |
|--|--------------|-----------------|-----------------|
|  | <b>Ratio</b> | <b>Lower CI</b> | <b>Upper CI</b> |
| <b>BSI</b>   | 1.00         | 0.70            | 1.75            |
| <b>UTI</b>   | 1.38         | 0.21            | 2.55            |
| <b>RESP</b>  | 4.06         | 1.38            | 6.73            |
| <b>SSI</b>   | 0.91         | 0.13            | 1.68            |
| <b>OTH</b>   | 0.67         | 0.06            | 1.27            |

| <b>Meticillin-resistant <i>S. aureus</i></b> |              |                 |                 |
|--|--------------|-----------------|-----------------|
|  | <b>Ratio</b> | <b>Lower CI</b> | <b>Upper CI</b> |
| <b>BSI</b>                                   | 1.00         | 0.80            | 1.34            |
| <b>UTI</b>                                   | 0.25         | 0.03            | 0.47            |
| <b>RESP</b>                                  | 1.65         | 0.86            | 2.45            |
| <b>SSI</b>                                   | 1.77         | 0.97            | 2.57            |
| <b>OTH</b>                                   | 1.62         | 0.89            | 2.36            |

\*When PPS did not provide information on given SPDAR, proxies were chosen, as detailed in the corresponding paragraph

## Addendum 2

Secondary BSI reducing factors for each SPDAR\*

| <b>Colistin-/carbapenem-/multidrug-resistant <i>Acinetobacter</i> spp.</b> |      |
|--|------|
| <b>BSI</b>   | 1    |
| <b>UTI</b>   | 0.03 |
| <b>RESP</b>  | 0.11 |
| <b>SSI</b>   | 0.08 |
| <b>OTH</b>   | 0.13 |

| <b>Colistin-/carbapenem-resistant <i>E. coli</i></b> |      |
|--|------|
| <b>BSI</b>   | 1    |
| <b>UTI</b>   | 0.25 |
| <b>RESP</b>  | 0.00 |
| <b>SSI</b>   | 0.00 |
| <b>OTH</b>   | 0.00 |

| <b>Third-generation cephalosporin-resistant <i>E. coli</i></b> |      |
|--|------|
| <b>BSI</b>   | 1    |
| <b>UTI</b>   | 0.16 |
| <b>RESP</b>  | 0.06 |
| <b>SSI</b>   | 0.13 |
| <b>OTH</b>   | 0.25 |

| <b>Vancomycin-resistant <i>E. faecalis</i> and <i>E. faecium</i></b> |      |
|--|------|
| <b>BSI</b>   | 1    |
| <b>UTI</b>   | 0.13 |
| <b>RESP</b>  | 0.00 |
| <b>SSI</b>   | 0.13 |
| <b>OTH</b>   | 0.25 |

| <b>Colistin-/carbapenem-resistant <i>K. pneumoniae</i></b> |      |
|--|------|
| <b>BSI</b>   | 1    |
| <b>UTI</b>   | 0.10 |
| <b>RESP</b>  | 0.19 |
| <b>SSI</b>   | 0.06 |
| <b>OTH</b>   | 0.18 |

| <b>Third-generation cephalosporin-resistant <i>K. pneumoniae</i></b> |      |
|--|------|
| <b>BSI</b>   | 1    |
| <b>UTI</b>   | 0.32 |
| <b>RESP</b>  | 0.06 |
| <b>SSI</b>   | 0.03 |
| <b>OTH</b>   | 0.10 |

| <b>Colistin-/carbapenem-/multidrug-resistant <i>P. aeruginosa</i></b> |      |
|---|------|
| <b>BSI</b>  | 1    |
| <b>UTI</b>  | 0.00 |
| <b>RESP</b>   | 0.08 |
| <b>SSI</b>  | 0.16 |
| <b>OTH</b>  | 0.12 |

| <b>Meticillin-resistant <i>S. aureus</i></b> |      |
|--|------|
| <b>BSI</b>                                   | 1    |
| <b>UTI</b>                                   | 0.00 |
| <b>RESP</b>                                  | 0.11 |
| <b>SSI</b>                                   | 0.09 |
| <b>OTH</b>                                   | 0.11 |

\*When PPS did not provide information on given SPDAR, proxies were chosen, as detailed in the corresponding paragraph

### Addendum 3

Number of blood culture sets tested/1 000 hospital inpatient days reported by EARS-Net participating hospitals from your country.

| Country        | Number of blood culture tests tested/1000 hospital inpatient days reported | Score<br>1.32 |
|----------------|--|---------------|
| Austria        | 15.7   | 1             |
| Belgium        | NA   | 0             |
| Bulgaria       | 8.2  | 1             |
| Croatia        | NA   | 0             |
| Cyprus         | 41.4   | 2             |
| Czech Republic | 16.6   | 2             |
| Denmark        | NA   | 0             |
| Estonia        | 17.8   | 2             |
| Finland        | NA   | 0             |
| France         | 86.5   | 2             |
| Germany        | 24.9   | 2             |
| Greece         | NA   | 0             |
| Hungary        | 8.4  | 1             |
| Iceland        | 43.1   | 2             |
| Ireland        | 52.9   | 2             |
| Italy          | NA   | 0             |
| Latvia         | 6.7  | 1             |
| Lithuania      | NA   | 0             |
| Luxembourg     | NA   | 0             |
| Malta          | 22.7   | 2             |
| Netherlands    | NA   | 0             |
| Norway         | 56.9   | 2             |
| Poland         | 32.4   | 2             |
| Portugal       | 64.6   | 2             |
| Romania        | NA   | 0             |
| Slovakia       | 20.1   | 2             |
| Slovenia       | 35.1   | 2             |
| Spain          | NA   | 0             |
| Sweden         | NA   | 0             |
| United Kingdom | 65.4   | 2             |

**Score (will be calculated by the LabCap team):**

0 = information not reported to EARS-Net

1 = low blood culture test utilisation rate/1000 patient days (first quartile)

2 = fair to high blood culture utilisation rate/1000 patient days (upper three quartiles)

## Addendum 4

### Imputation methodology applied for each antibiotic resistance-bacterium combination in each country for the redistribution of cases reported to EARS-Net with unknown age and/or sex cases

|                | 3GCREC | CREC | CoIREC | 3GCRKP | CRKP | CoIRKP | MDRACI | CRACI | CoIRACI | MDRPA | CRPA | CoIRPA | MRSA | VRE | PRSP | PMRSP |
|----------------|--------|------|--------|--------|------|--------|--------|-------|---------|-------|------|--------|------|-----|------|-------|
| Austria        | 😊      | 😊    | 😊      | 😊      | 😊    | 😊      | 😊      | 😊     | 😊       | 😊     | 😊    | 😊      | 😊    | 😊   | 😊    | 😊     |
| Belgium        | 😊      | 😊    | 😊      | 😊      | 😊    | 😊      | 😊      | 😊     | 😊       | 😊     | 😊    | 😊      | 😊    | 😊   | 😊    | 😊     |
| Bulgaria       | 😊      | 😊    | 😊      | 😊      | 😊    | 😊      | 😊      | 😊     | 😊       | 😊     | 😊    | 😊      | 😊    | 😊   | 😊    | 😊     |
| Cyprus         | 😊      | 😊    | 😊      | 😊      | 😊    | 😊      | 😊      | 😊     | 😞       | 😊     | 😊    | 😊      | 😊    | 😊   | 😊    | 😞     |
| Czech Republic | 😊      | 😊    | 😊      | 😊      | 😊    | 😊      | 😊      | 😊     | 😊       | 😊     | 😊    | 😊      | 😊    | 😊   | 😊    | 😊     |
| Germany        | 😊      | 😊    | 😊      | 😊      | 😊    | 😊      | 😊      | 😊     | 😊       | 😊     | 😊    | 😊      | 😊    | 😊   | 😊    | 😊     |
| Denmark        | 😊      | 😊    | 😊      | 😊      | 😊    | 😊      | 😊      | 😊     | 😊       | 😊     | 😊    | 😊      | 😊    | 😊   | 😞    | 😞     |
| Estonia        | 😊      | 😊    | 😊      | 😊      | 😊    | 😊      | 😊      | 😊     | 😊       | 😊     | 😊    | 😊      | 😊    | 😊   | 😊    | 😊     |
| Greece         | 😞      | 😞    | 😞      | 😞      | 😞    | 😞      | 😞      | 😞     | 😞       | 😞     | 😞    | 😞      | 😞    | 😞   | NA   | NA    |
| Spain          | 😊      | 😊    | 😊      | 😊      | 😊    | 😊      | 😊      | 😊     | 😊       | 😊     | 😊    | 😊      | 😊    | 😊   | 😊    | 😊     |
| Finland        | 😊      | 😊    | 😊      | 😊      | 😊    | 😊      | 😊      | 😊     | 😊       | 😊     | 😊    | 😊      | 😊    | 😊   | 😊    | 😊     |
| France         | 😞      | 😞    | 😊      | 😞      | 😊    | 😊      | 😊      | 😊     | 😊       | 😞     | 😊    | 😊      | 😞    | 😞   | 😊    | 😊     |
| Croatia        | 😊      | 😊    | 😊      | 😊      | 😊    | 😊      | 😊      | 😊     | 😊       | 😊     | 😊    | 😊      | 😊    | 😊   | 😊    | 😊     |
| Hungary        | 😊      | 😊    | 😊      | 😊      | 😊    | 😊      | 😊      | 😊     | 😊       | 😊     | 😊    | 😊      | 😊    | 😊   | 😊    | 😊     |
| Ireland        | 😊      | 😊    | 😊      | 😊      | 😊    | 😊      | 😊      | 😊     | 😊       | 😊     | 😊    | 😊      | 😊    | 😊   | 😊    | 😊     |
| Iceland        | 😊      | 😊    | 😊      | 😊      | 😊    | 😊      | 😊      | 😊     | 😊       | 😊     | 😊    | 😊      | 😊    | 😊   | 😊    | 😊     |
| Italy          | 😞      | 😞    | 😞      | 😞      | 😞    | 😞      | 😞      | 😞     | 😞       | 😞     | 😞    | 😞      | 😞    | 😞   | 😞    | 😞     |
| Lithuania      | 😞      | 😊    | 😊      | 😞      | 😊    | 😊      | 😞      | 😞     | 😊       | 😞     | 😞    | 😊      | 😞    | 😞   | 😞    | 😞     |
| Luxembourg     | 😊      | 😊    | 😊      | 😊      | 😊    | 😊      | 😊      | 😊     | 😊       | 😊     | 😊    | 😊      | 😊    | 😊   | 😊    | 😊     |
| Latvia         | 😊      | 😊    | 😊      | 😊      | 😊    | 😊      | 😊      | 😊     | 😊       | 😊     | 😊    | 😊      | 😊    | 😊   | 😊    | 😊     |
| Malta          | 😊      | 😊    | 😊      | 😊      | 😊    | 😊      | 😊      | 😊     | 😊       | 😊     | 😊    | 😊      | 😊    | 😊   | 😊    | 😊     |
| Netherlands    | 😊      | 😊    | 😊      | 😊      | 😊    | 😊      | 😊      | 😊     | 😊       | 😊     | 😊    | 😊      | 😊    | 😊   | 😊    | 😊     |
| Norway         | 😊      | 😊    | 😊      | 😊      | 😊    | 😊      | 😊      | 😊     | 😊       | 😊     | 😊    | 😊      | 😊    | 😊   | 😊    | 😊     |
| Poland         | 😊      | 😊    | 😊      | 😊      | 😊    | 😊      | 😊      | 😊     | 😊       | 😊     | 😊    | 😊      | 😊    | 😊   | 😊    | 😊     |
| Portugal       | 😊      | 😊    | 😊      | 😊      | 😊    | 😊      | 😊      | 😊     | 😊       | 😊     | 😊    | 😊      | 😊    | 😊   | 😊    | 😊     |
| Romania        | 😊      | 😊    | 😊      | 😊      | 😊    | 😊      | 😊      | 😊     | 😊       | 😊     | 😊    | 😊      | 😊    | 😊   | 😊    | 😊     |
| Sweden         | 😊      | 😊    | 😊      | 😊      | 😊    | 😊      | 😊      | 😊     | 😊       | 😊     | 😊    | 😊      | 😊    | 😊   | 😊    | 😊     |
| Slovenia       | 😊      | 😊    | 😊      | 😊      | 😊    | 😊      | 😊      | 😊     | 😊       | 😊     | 😊    | 😊      | 😊    | 😊   | 😊    | 😊     |
| Slovakia       | 😊      | 😊    | 😊      | 😊      | 😊    | 😊      | 😊      | 😊     | 😊       | 😊     | 😊    | 😊      | 😊    | 😊   | 😊    | 😊     |
| United Kingdom | 😊      | 😊    | 😊      | 😊      | 😊    | 😊      | 😊      | 😊     | 😊       | 😊     | 😊    | 😊      | 😊    | 😊   | 😊    | 😊     |

- 😊 No unknown cases reported
- 😊 Less than 40% of reported cases with unknown age and/or sex: redistribution of unknown cases based on imputation from the country-specific known cases for the same antibiotic resistance-bacterium combination
- 😞 More than 40% of reported data with unknown age and/or sex: redistribution of unknown cases based on imputation from EU/EEA cumulative known cases for the same antibiotic resistance-bacterium combination

Greece did not report data on *S. pneumoniae* isolates to EARS-Net in 2015

## Burden of antimicrobial resistance

# **GATHER checklist and further analysis on MRSA and attribution as healthcare-associated infections**

Written by Alessandro Cassini with contributions from Carl Suetens, Liselotte Diaz Högberg, Diamantis Plachouras, and Dominique Monnet

## Contents

|   |     |
|---|-----|
| List of abbreviations .....   | 215 |
| 1. Estimation of proportion of infections due to antimicrobial resistant organisms that are healthcare-associated ..... | 216 |
| 2. Further analysis on MRSA trends between 2007 and 2015.....   | 218 |
| 3. GATHER checklist.....  | 220 |

## List of abbreviations

|          |   |
|----------|---|
| 3GCREC   | third-generation cephalosporin-resistant <i>E. coli</i>   |
| 3GCRKP   | third-generation cephalosporin-resistant <i>K. pneumoniae</i>   |
| AMR      | antimicrobial resistance  |
| BSI      | bloodstream infection   |
| CAI      | Community-associated infections   |
| CI       | confidence interval   |
| ColRACI  | colistin-resistant <i>Acinetobacter</i> spp.  |
| ColREC   | colistin-resistant <i>E. coli</i>   |
| ColRKP   | colistin-resistant <i>K. pneumoniae</i>   |
| ColRPA   | colistin-resistant <i>P. aeruginosa</i>   |
| CRACI    | carbapenem-resistant <i>Acinetobacter</i> spp.  |
| CREC     | carbapenem-resistant <i>E. coli</i>   |
| CRKP     | carbapenem-resistant <i>K. pneumoniae</i>   |
| CRPA     | carbapenem-resistant <i>P. aeruginosa</i>   |
| CSF      | cerebral spine fluid  |
| DALY     | disability-adjusted life years  |
| EARS-Net | European Antimicrobial Resistance Surveillance Network  |
| EEA      | European Economic Area  |
| EU       | European Union  |
| HAI      | healthcare-associated infection   |
| LOS      | length of stay  |
| MDR      | multidrug-resistant   |
| MDRACI   | multidrug-resistant <i>Acinetobacter</i> spp  |
| MDRPA    | multidrug-resistant <i>P. aeruginosa</i>  |
| MRSA     | meticillin-resistant <i>Staphylococcus aureus</i>   |
| MS       | Member State  |
| OECD     | Organisation for Economic Co-operation and Development  |
| OTH      | other infection site including digestive tract infections, skin and soft tissue infections (SSTI), eye, ear, nose or mouth infections, bone and joint infections, cardiovascular infections, reproductive tract infections and other less frequent infections |
| PMRSP    | penicillin- and macrolide-resistant <i>S. pneumoniae</i>  |
| PPS      | point prevalence survey of healthcare-associated infections and antimicrobial use in acute care hospitals   |
| PRSP     | penicillin-resistant <i>S. pneumoniae</i> ;   |
| RESP     | respiratory infections (including pneumonia, and low respiratory tract infection)   |
| S-BSI    | secondary BSI   |
| SP       | specified pathogens   |
| SPDAR    | specified pathogens with defined antimicrobial resistance   |
| SSI      | surgical site infection   |
| UTI      | urinary tract infection   |
| VRE      | vancomycin-resistant enterococci  |



## Estimation of proportion of infections due to antimicrobial resistant organisms that are healthcare-associated

All *S. pneumoniae* (penicillin-resistant, combined macrolide- and penicillin-resistant) were assumed to be 100% community-associated infections (CAIs), while the following EARS-Net pathogens were assumed to be 100% HAIs:

- All infections resistant to carbapenems and/or colistin;
- *Acinetobacter* spp.;
- *Pseudomonas aeruginosa*;
- *Enterococcus faecalis* and *E. faecium*.

We estimated the proportion of HAIs and CAIs for the following infections due to antimicrobial resistant organisms:

- Third-generation cephalosporin-resistant *Klebsiella pneumoniae* and *Escherichia coli* (excluding those resistant to colistin and/or carbapenem);
- Meticillin-resistant *Staphylococcus aureus*.

Information from EARS-Net was initially used to split HAIs from CAIs. EARS-Net information on date of hospital admission is available for a minority of cases, varying for each SP and across countries. In 2015 the proportion of all EARS-Net cases with information on date of hospitalisation was around 23%. Information on the time of admission (hour: minute) is not available. Therefore, for each group of infections due to antimicrobial resistant organisms, the EU/EEA cumulative number of cases notified to EARS-Net with information on date of hospitalisation was used to estimate the proportion of HAIs and CAIs. HAI was defined as patient with positive isolate on day 3 or more, based on date of hospital admission. CAI was defined as a patient with a positive isolate before day 3 of admission.

However, as EARS-Net does not provide information on previous history of hospitalisation (e.g. readmission and patient transfer) the number is likely to underestimate the true proportion of HAIs. Therefore, for each specific pathogen/resistance combination, the resulting HAI/CAI proportion was further adjusted by applying the PPS percentage of HAIs present on hospital admission (assuming that a certain percentage of HAIs with recent discharge from a hospital [within 48 hours] was misclassified as CAI in EARS-Net).

Therefore, considering that  $HAI_{EARS-Net} = HAI_{corrected} - x\% * HAI_{corrected}$  we used the following formula:

$$HAI_{corrected} = HAI_{EARS-Net} / (1 - x)$$

With x being the percentage of HAIs present on hospital admission from the PPS database. The resulting HAI proportions were:

- Third-generation cephalosporin-resistant *Klebsiella pneumoniae* (excluding those resistant to colistin and/or carbapenem):
  - 68% (66-70%) were considered HAIs
- Third-generation cephalosporin-resistant *Escherichia coli* (excluding those resistant to colistin and/or carbapenem):
  - 43% (41-44%) were considered HAIs
- Meticillin-resistant *Staphylococcus aureus*:
  - 68% (66-70%) were considered HAIs

Our estimation of the proportion of infections with antibiotic-resistant bacteria that were considered HAIs or CAIs was inherently limited by our a priori classification of infections caused by several bacterial species or any isolate resistant to colistin or to carbapenem as 100% HAI, given the limited availability and quality of the data on the likely individual place of acquisition of the infections reported to EARS-Net. This over-simplification has introduced a misclassification bias towards overestimating the HAI fraction of total burden of disease.

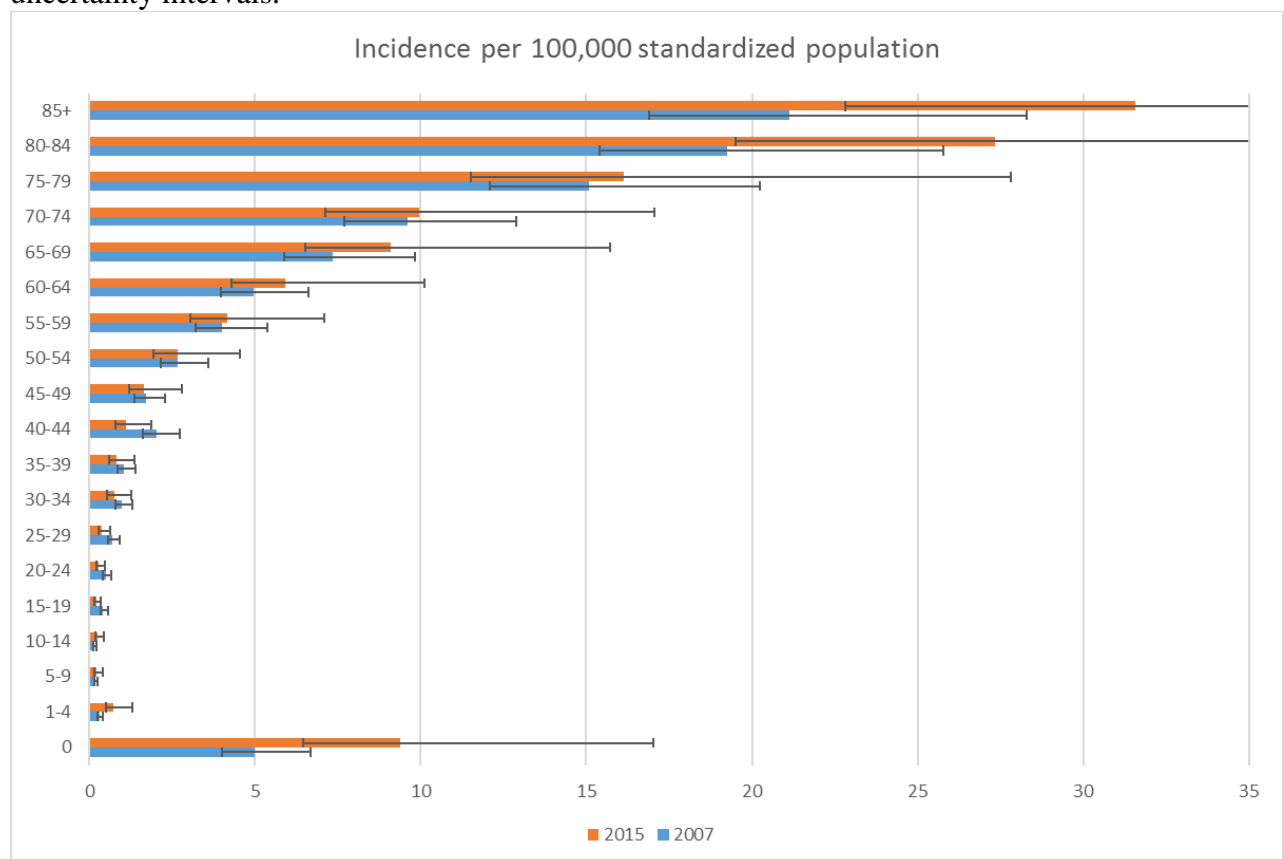
Moreover, the data from EARS-Net do not distinguish between CAI and community onset infections. If not adjusted for, this might cause an underestimation of the true proportion of HAIs, as re-admissions with a HAI might be misclassified as CAI. We used the PPS percentage of HAIs present on hospital admission for each specific pathogen/resistance combination to adjust the number of CAIs reported from EARS-Net, hence limiting the impact of CAI misclassification.

## Further analysis on MRSA trends between 2007 and 2015

As part of this study, the methodology developed to estimate the burden of AMR in 2015 was used with 2007 EARS-Net data in order to compare the epidemiological situation and trends across time.

From 2007 to 2015, the proportion of *Staphylococcus aureus* isolates that were resistant to meticillin in the EU/EEA decreased from 26.6% to 16.8%. The 2007 population-weighted EU/EEA mean percentage was determined by applying population-based weights to each country's data before calculating the arithmetic mean for all reporting countries. Country weightings were used to adjust for imbalances in reporting propensity and population coverage, as the total number of reported isolates by country in most cases does not reflect the population size. The weighting applied to each national data point represented the proportion of the country's population out of the total population of all countries included in the calculation. Annual population data were retrieved from the Eurostat online database. However, in our study we found that between 2007 and 2015 the incidence of MRSA increased by 23% (6-41%). In order to partly explore the reasons behind this apparent discrepancy, we analysed the age-specific incidence in 2007 and 2015, see Figure 1.

Figure 1: age-group specific incidence rates of MRSA in 2007 and 2015. Median and 95% uncertainty intervals.



From Figure 1 it seems that the increase was experienced mainly in infants (and children under 4 years old) and in the elderly population (starting from those over 55 years old).

A number of reasons might explain the observed pattern:

- Increase of participating laboratories reporting EARS-Net and consequent country coverage;
- Increase in incidence of *S. aureus*

- Demographic increase in the elderly – ageing of the population which are more vulnerable and at higher chance of developing diseases, hence increasing the number of those at risk;
- Improvement of the neonatal services, increasing the survival of at-risk infants, hence increasing a vulnerable population at risk for infections;

The increase of MRSA incidence was also described in other studies:

1. Sarvikivi E, Ollgren J, Lyytikäinen O. Trends and outcome of healthcare-associated and community-onset bloodstream infections due to *Staphylococcus aureus* in Finland 2004-2015. European Scientific Conference on Applied Infectious Disease Epidemiology; 2017; Stockholm.
2. Swedres-Svarm 2016. Consumption of antibiotics and occurrence of resistance in Sweden. Solna/Uppsala ISSN1650-6332.

## GATHER checklist



### Checklist of information that should be included in new reports of global health estimates

| Item #  | Checklist item  | Reported in manuscript and/or appendixes  |
|---|---|---|
| <b>Objectives and funding</b>   |   |   |
| 1   | Define the indicator(s), populations (including age, sex, and geographic entities), and time period(s) for which estimates were made.   | Information in the Methods section under “Study design and outcome measure” (indicator) and under “Study population and estimation of incidence” (population including age, sex, geography and time period) |
| 2   | List the funding sources for the work.  | Statement available in the manuscript (“No specific funding was allocated for this study, which was conducted as part of routine work of ECDC and participating institutions.”)                             |
| <b>Data Inputs</b>  |   |   |
| <i>For all data inputs from multiple sources that are synthesized as part of the study:</i>           |   |   |
| 3   | Describe how the data were identified and how the data were accessed.   | Information available in the Methods section  |
| 4   | Specify the inclusion and exclusion criteria. Identify all ad-hoc exclusions.   | Information available in the Methods section  |
| 5   | Provide information on all included data sources and their main characteristics. For each data source used, report reference information or contact name/institution, population represented, data collection method, year(s) of data collection, sex and age range, diagnostic criteria or measurement method, and sample size, as relevant. | Information available in the Methods section. Limitations related to data source and quality are available at the end of the Discussion section.  |
| 6   | Identify and describe any categories of input data that have potentially important biases (e.g., based on characteristics listed in item 5).  | Information available in the Methods section. Limitations related to data source and quality are available at the end of the Discussion section.  |
| <i>For data inputs that contribute to the analysis but were not synthesized as part of the study:</i> |   |   |

|                               |   |   |
|-------------------------------|---|---|
| 7                             | Describe and give sources for any other data inputs.  | Information available in the Methods section. Limitations related to data source and quality are available at the end of the Discussion section.  |
| <i>For all data inputs:</i>   |   |   |
| 8                             | Provide all data inputs in a file format from which data can be efficiently extracted (e.g., a spreadsheet rather than a PDF), including all relevant meta-data listed in item 5. For any data inputs that cannot be shared because of ethical or legal reasons, such as third-party ownership, provide a contact name or the name of the institution that retains the right to the data. | Information available in the Methods section and in Supplementary appendixes. Case-based data is not shared for ethical reasons but can be requested to country experts (“Burden of AMR Collaborative Group”) |
| <b>Data analysis</b>          |   |   |
| 9                             | Provide a conceptual overview of the data analysis method. A diagram may be helpful.  | Information available in the Methods section and in Supplementary appendixes.   |
| 10                            | Provide a detailed description of all steps of the analysis, including mathematical formulae. This description should cover, as relevant, data cleaning, data pre-processing, data adjustments and weighting of data sources, and mathematical or statistical model(s).   | Information available in the Methods section and in Supplementary appendixes.   |
| 11                            | Describe how candidate models were evaluated and how the final model(s) were selected.  | Information available in the Methods section and in Supplementary appendixes.   |
| 12                            | Provide the results of an evaluation of model performance, if done, as well as the results of any relevant sensitivity analysis.  | Information available in the Methods section and in Supplementary appendixes.   |
| 13                            | Describe methods for calculating uncertainty of the estimates. State which sources of uncertainty were, and were not, accounted for in the uncertainty analysis.  | Information available in the Methods section and in Supplementary appendixes. Limitations related to data source and quality are available at the end of the Discussion section.                              |
| 14                            | State how analytic or statistical source code used to generate estimates can be accessed.   | Information available in the Methods section and in Supplementary appendixes.   |
| <b>Results and Discussion</b> |   |   |
| 15                            | Provide published estimates in a file format from which data can be efficiently extracted.  | Information available in the Results and Discussion sections, and in Supplementary appendixes.  |
| 16                            | Report a quantitative measure of the uncertainty of the estimates (e.g. uncertainty intervals).   | Information available in the Results and Discussion sections, and in Supplementary appendixes.  |
| 17                            | Interpret results in light of existing evidence. If updating a previous set of estimates, describe the reasons for changes in estimates.  | Information available in the Discussion section and in Supplementary appendixes.  |

|           |  |  |
|-----------|--|--|
| <b>18</b> | Discuss limitations of the estimates. Include a discussion of any modelling assumptions or data limitations that affect interpretation of the estimates. | Information available in the Discussion section and in Supplementary appendixes. |
|-----------|--|--|

## Burden of antimicrobial resistance

# Country specific results

Alessandro Cassini







# Burden of antimicrobial resistance

Country specific results

Alessandro Cassini



|          |   |
|----------|---|
| 3GCREC   | third-generation cephalosporin-resistant <i>E. coli</i>   |
| 3GCRKP   | third-generation cephalosporin-resistant <i>K. pneumoniae</i>   |
| AMR      | antimicrobial resistance  |
| BSI      | bloodstream infection   |
| CAI      | Community-associated infections   |
| CI       | confidence interval   |
| ColRACI  | colistin-resistant <i>Acinetobacter</i> spp.  |
| ColREC   | colistin-resistant <i>E. coli</i>   |
| ColRKP   | colistin-resistant <i>K. pneumoniae</i>   |
| ColRPA   | colistin-resistant <i>P. aeruginosa</i>   |
| CRACI    | carbapenem-resistant <i>Acinetobacter</i> spp.  |
| CREC     | carbapenem-resistant <i>E. coli</i>   |
| CRKP     | carbapenem-resistant <i>K. pneumoniae</i>   |
| CRPA     | carbapenem-resistant <i>P. aeruginosa</i>   |
| CSF      | cerebral spine fluid  |
| DALY     | disability-adjusted life years  |
| EARS-Net | European Antimicrobial Resistance Surveillance Network  |
| EEA      | European Economic Area  |
| EU       | European Union  |
| HAI      | healthcare-associated infection   |
| LOS      | length of stay  |
| MDR      | multidrug-resistant   |
| MDRACI   | multidrug-resistant <i>Acinetobacter</i> spp  |
| MDRPA    | multidrug-resistant <i>P. aeruginosa</i>  |
| MRSA     | meticillin-resistant <i>Staphylococcus aureus</i>   |
| MS       | Member State  |
| OECD     | Organisation for Economic Co-operation and Development  |
| OTH      | other infection site including digestive tract infections, skin and soft tissue infections (SSTI), eye, ear, nose or mouth infections, bone and joint infections, cardiovascular infections, reproductive tract infections and other less frequent infections |
| PMRSP    | penicillin- and macrolide-resistant <i>S. pneumoniae</i>  |
| PPS      | point prevalence survey of healthcare-associated infections and antimicrobial use in acute care hospitals   |
| PRSP     | penicillin-resistant <i>S. pneumoniae</i> ;   |
| RESP     | respiratory infections (including pneumonia, and low respiratory tract infection)   |
| S-BSI    | secondary BSI   |
| SP       | specified pathogens   |
| SPDAR    | specified pathogens with defined antimicrobial resistance   |
| SSI      | surgical site infection   |
| UTI      | urinary tract infection   |
| VRE      | vancomycin-resistant enterococci  |



|               | 2020  |        | 2021  |        | 2022  |        | 2023  |        | 2024  |        | 2025  |        | 2026  |        | 2027  |        | 2028  |        | 2029  |        | 2030  |        | 2031  |        | 2032  |        | 2033  |        | 2034  |        | 2035  |        | 2036  |        | 2037  |        | 2038  |        | 2039  |        | 2040  |        |       |        |       |        |       |        |       |        |       |        |       |        |       |        |       |        |       |        |       |        |       |        |       |        |       |        |       |        |       |        |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |      |
|---------------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|--------|------|
|               | Value | %      | Value | %      | Value | %      | Value | %      | Value | %      | Value | %      | Value | %      | Value | %      | Value | %      | Value | %      | Value | %      | Value | %      | Value | %      | Value | %      | Value | %      | Value | %      | Value | %      | Value | %      | Value | %      | Value | %      | Value | %      |       |        |       |        |       |        |       |        |       |        |       |        |       |        |       |        |       |        |       |        |       |        |       |        |       |        |       |        |       |        |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |       |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |         |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |          |        |      |
| Member States | 4737  | 124.76 | 5871  | 131.52 | 7107  | 148.36 | 8344  | 176.33 | 9581  | 202.30 | 10818 | 228.17 | 12055 | 254.14 | 13292 | 279.11 | 14529 | 304.08 | 15766 | 329.05 | 17003 | 354.02 | 18240 | 379.00 | 19477 | 404.00 | 20714 | 429.00 | 21951 | 454.00 | 23188 | 479.00 | 24425 | 504.00 | 25662 | 529.00 | 26899 | 554.00 | 28136 | 579.00 | 29373 | 604.00 | 30610 | 629.00 | 31847 | 654.00 | 33084 | 679.00 | 34321 | 704.00 | 35558 | 729.00 | 36795 | 754.00 | 38032 | 779.00 | 39269 | 804.00 | 40506 | 829.00 | 41743 | 854.00 | 43000 | 879.00 | 44237 | 904.00 | 45481 | 929.00 | 46718 | 954.00 | 48005 | 979.00 | 49242 | 1004.00 | 50479 | 1029.00 | 51716 | 1054.00 | 52953 | 1079.00 | 54190 | 1104.00 | 55427 | 1129.00 | 56664 | 1154.00 | 57901 | 1179.00 | 59138 | 1204.00 | 60375 | 1229.00 | 61612 | 1254.00 | 62849 | 1279.00 | 64086 | 1304.00 | 65323 | 1329.00 | 66560 | 1354.00 | 67797 | 1379.00 | 69034 | 1404.00 | 70271 | 1429.00 | 71508 | 1454.00 | 72745 | 1479.00 | 73982 | 1504.00 | 75219 | 1529.00 | 76456 | 1554.00 | 77693 | 1579.00 | 78930 | 1604.00 | 80167 | 1629.00 | 81404 | 1654.00 | 82641 | 1679.00 | 83878 | 1704.00 | 85115 | 1729.00 | 86352 | 1754.00 | 87589 | 1779.00 | 88826 | 1804.00 | 90063 | 1829.00 | 91300 | 1854.00 | 92537 | 1879.00 | 93774 | 1904.00 | 95011 | 1929.00 | 96248 | 1954.00 | 97485 | 1979.00 | 98722 | 2004.00 | 100000 | 2029.00 | 101237 | 2054.00 | 102474 | 2079.00 | 103711 | 2104.00 | 104948 | 2129.00 | 106185 | 2154.00 | 107422 | 2179.00 | 108659 | 2204.00 | 109896 | 2229.00 | 111133 | 2254.00 | 112370 | 2279.00 | 113607 | 2304.00 | 114844 | 2329.00 | 116081 | 2354.00 | 117318 | 2379.00 | 118555 | 2404.00 | 119792 | 2429.00 | 121029 | 2454.00 | 122266 | 2479.00 | 123503 | 2504.00 | 124740 | 2529.00 | 125977 | 2554.00 | 127214 | 2579.00 | 128451 | 2604.00 | 129688 | 2629.00 | 130925 | 2654.00 | 132162 | 2679.00 | 133399 | 2704.00 | 134636 | 2729.00 | 135873 | 2754.00 | 137110 | 2779.00 | 138347 | 2804.00 | 139584 | 2829.00 | 140821 | 2854.00 | 142058 | 2879.00 | 143295 | 2904.00 | 144532 | 2929.00 | 145769 | 2954.00 | 147006 | 2979.00 | 148243 | 3004.00 | 149480 | 3029.00 | 150717 | 3054.00 | 151954 | 3079.00 | 153191 | 3104.00 | 154428 | 3129.00 | 155665 | 3154.00 | 156902 | 3179.00 | 158139 | 3204.00 | 159376 | 3229.00 | 160613 | 3254.00 | 161850 | 3279.00 | 163087 | 3304.00 | 164324 | 3329.00 | 165561 | 3354.00 | 166798 | 3379.00 | 168035 | 3404.00 | 169272 | 3429.00 | 170509 | 3454.00 | 171746 | 3479.00 | 172983 | 3504.00 | 174220 | 3529.00 | 175457 | 3554.00 | 176694 | 3579.00 | 177931 | 3604.00 | 179168 | 3629.00 | 180405 | 3654.00 | 181642 | 3679.00 | 182879 | 3704.00 | 184116 | 3729.00 | 185353 | 3754.00 | 186590 | 3779.00 | 187827 | 3804.00 | 189064 | 3829.00 | 190301 | 3854.00 | 191538 | 3879.00 | 192775 | 3904.00 | 194012 | 3929.00 | 195249 | 3954.00 | 196486 | 3979.00 | 197723 | 4004.00 | 198960 | 4029.00 | 200197 | 4054.00 | 201434 | 4079.00 | 202671 | 4104.00 | 203908 | 4129.00 | 205145 | 4154.00 | 206382 | 4179.00 | 207619 | 4204.00 | 208856 | 4229.00 | 210093 | 4254.00 | 211330 | 4279.00 | 212567 | 4304.00 | 213804 | 4329.00 | 215041 | 4354.00 | 216278 | 4379.00 | 217515 | 4404.00 | 218752 | 4429.00 | 220000 | 4454.00 | 221237 | 4479.00 | 222474 | 4504.00 | 223711 | 4529.00 | 224948 | 4554.00 | 226185 | 4579.00 | 227422 | 4604.00 | 228659 | 4629.00 | 229896 | 4654.00 | 231133 | 4679.00 | 232370 | 4704.00 | 233607 | 4729.00 | 234844 | 4754.00 | 236081 | 4779.00 | 237318 | 4804.00 | 238555 | 4829.00 | 239792 | 4854.00 | 241029 | 4879.00 | 242266 | 4904.00 | 243503 | 4929.00 | 244740 | 4954.00 | 245977 | 4979.00 | 247214 | 5004.00 | 248451 | 5029.00 | 249688 | 5054.00 | 250925 | 5079.00 | 252162 | 5104.00 | 253399 | 5129.00 | 254636 | 5154.00 | 255873 | 5179.00 | 257110 | 5204.00 | 258347 | 5229.00 | 259584 | 5254.00 | 260821 | 5279.00 | 262058 | 5304.00 | 263295 | 5329.00 | 264532 | 5354.00 | 265769 | 5379.00 | 267006 | 5404.00 | 268243 | 5429.00 | 269480 | 5454.00 | 270717 | 5479.00 | 271954 | 5504.00 | 273191 | 5529.00 | 274428 | 5554.00 | 275665 | 5579.00 | 276902 | 5604.00 | 278139 | 5629.00 | 279376 | 5654.00 | 280613 | 5679.00 | 281850 | 5704.00 | 283087 | 5729.00 | 284324 | 5754.00 | 285561 | 5779.00 | 286798 | 5804.00 | 288035 | 5829.00 | 289272 | 5854.00 | 290509 | 5879.00 | 291746 | 5904.00 | 292983 | 5929.00 | 294220 | 5954.00 | 295457 | 5979.00 | 296694 | 6004.00 | 297931 | 6029.00 | 299168 | 6054.00 | 300405 | 6079.00 | 301642 | 6104.00 | 302879 | 6129.00 | 304116 | 6154.00 | 305353 | 6179.00 | 306590 | 6204.00 | 307827 | 6229.00 | 309064 | 6254.00 | 310301 | 6279.00 | 311538 | 6304.00 | 312775 | 6329.00 | 314012 | 6354.00 | 315249 | 6379.00 | 316486 | 6404.00 | 317723 | 6429.00 | 318960 | 6454.00 | 320197 | 6479.00 | 321434 | 6504.00 | 322671 | 6529.00 | 323908 | 6554.00 | 325145 | 6579.00 | 326382 | 6604.00 | 327619 | 6629.00 | 328856 | 6654.00 | 330093 | 6679.00 | 331330 | 6704.00 | 332567 | 6729.00 | 333804 | 6754.00 | 335041 | 6779.00 | 336278 | 6804.00 | 337515 | 6829.00 | 338752 | 6854.00 | 340000 | 6879.00 | 341237 | 6904.00 | 342474 | 6929.00 | 343711 | 6954.00 | 344948 | 6979.00 | 346185 | 7004.00 | 347422 | 7029.00 | 348659 | 7054.00 | 349896 | 7079.00 | 351133 | 7104.00 | 352370 | 7129.00 | 353607 | 7154.00 | 354844 | 7179.00 | 356081 | 7204.00 | 357318 | 7229.00 | 358555 | 7254.00 | 359792 | 7279.00 | 361029 | 7304.00 | 362266 | 7329.00 | 363503 | 7354.00 | 364740 | 7379.00 | 365977 | 7404.00 | 367214 | 7429.00 | 368451 | 7454.00 | 369688 | 7479.00 | 370925 | 7504.00 | 372162 | 7529.00 | 373399 | 7554.00 | 374636 | 7579.00 | 375873 | 7604.00 | 377110 | 7629.00 | 378347 | 7654.00 | 379584 | 7679.00 | 380821 | 7704.00 | 382058 | 7729.00 | 383295 | 7754.00 | 384532 | 7779.00 | 385769 | 7804.00 | 387006 | 7829.00 | 388243 | 7854.00 | 389480 | 7879.00 | 390717 | 7904.00 | 391954 | 7929.00 | 393191 | 7954.00 | 394428 | 7979.00 | 395665 | 8004.00 | 396902 | 8029.00 | 398139 | 8054.00 | 399376 | 8079.00 | 400613 | 8104.00 | 401850 | 8129.00 | 403087 | 8154.00 | 404324 | 8179.00 | 405561 | 8204.00 | 406798 | 8229.00 | 408035 | 8254.00 | 409272 | 8279.00 | 410509 | 8304.00 | 411746 | 8329.00 | 412983 | 8354.00 | 414220 | 8379.00 | 415457 | 8404.00 | 416694 | 8429.00 | 417931 | 8454.00 | 419168 | 8479.00 | 420405 | 8504.00 | 421642 | 8529.00 | 422879 | 8554.00 | 424116 | 8579.00 | 425353 | 8604.00 | 426590 | 8629.00 | 427827 | 8654.00 | 429064 | 8679.00 | 430301 | 8704.00 | 431538 | 8729.00 | 432775 | 8754.00 | 434012 | 8779.00 | 435249 | 8804.00 | 436486 | 8829.00 | 437723 | 8854.00 | 438960 | 8879.00 | 440197 | 8904.00 | 441434 | 8929.00 | 442671 | 8954.00 | 443908 | 8979.00 | 445145 | 9004.00 | 446382 | 9029.00 | 447619 | 9054.00 | 448856 | 9079.00 | 450093 | 9104.00 | 451330 | 9129.00 | 452567 | 9154.00 | 453804 | 9179.00 | 455041 | 9204.00 | 456278 | 9229.00 | 457515 | 9254.00 | 458752 | 9279.00 | 459989 | 9304.00 | 461226 | 9329.00 | 462463 | 9354.00 | 463700 | 9379.00 | 464937 | 9404.00 | 466174 | 9429.00 | 467411 | 9454.00 | 468648 | 9479.00 | 469885 | 9504.00 | 471122 | 9529.00 | 472359 | 9554.00 | 473596 | 9579.00 | 474833 | 9604.00 | 476070 | 9629.00 | 477307 | 9654.00 | 478544 | 9679.00 | 479781 | 9704.00 | 481018 | 9729.00 | 482255 | 9754.00 | 483492 | 9779.00 | 484729 | 9804.00 | 485966 | 9829.00 | 487203 | 9854.00 | 488440 | 9879.00 | 489677 | 9904.00 | 490914 | 9929.00 | 492151 | 9954.00 | 493388 | 9979.00 | 494625 | 10004.00 | 495862 | 10029.00 | 497099 | 10054.00 | 498336 | 10079.00 | 499573 | 10104.00 | 500810 | 10129.00 | 502047 | 10154.00 | 503284 | 10179.00 | 504521 | 10204.00 | 505758 | 10229.00 | 506995 | 10254.00 | 508232 | 10279.00 | 509469 | 10304.00 | 510706 | 10329.00 | 511943 | 10354.00 | 513180 | 10379.00 | 514417 | 10404.00 | 515654 | 10429.00 | 516891 | 10454.00 | 518128 | 10479.00 | 519365 | 10504.00 | 520602 | 10529.00 | 521839 | 10554.00 | 523076 | 10579.00 | 524313 | 10604.00 | 525550 | 10629.00 | 526787 | 10654.00 | 528024 | 10679.00 | 529261 | 10704.00 | 530498 | 10729.00 | 531735 | 10754.00 | 532972 | 10779.00 | 534209 | 10804.00 | 535446 | 10829.00 | 536683 | 10854.00 | 537920 | 10879.00 | 539157 | 10904.00 | 540394 | 10929.00 | 541631 | 10954.00 | 542868 | 10979.00 | 544105 | 11004.00 | 545342 | 11029.00 | 546579 | 11054.00 | 547816 | 11079.00 | 549053 | 11104.00 | 550290 | 11129.00 | 551527 | 11154.00 | 552764 | 11179.00 | 554001 | 11204.00 | 555238 | 11229.00 | 556475 | 11254.00 | 557712 | 11279.00 | 558949 | 11304.00 | 560186 | 11329.00 | 561423 | 11354.00 | 562660 | 11379.00 | 563897 | 11404.00 | 565134 | 11429.00 | 566371 | 11454.00 | 567608 | 11479.00 | 568845 | 11504.00 | 570082 | 11529.00 | 571319 | 11554.00 | 572556 | 11579.00 | 573793 | 11604.00 | 575030 | 11629.00 | 576267 | 11654.00 | 577504 | 11679.00 | 578741 | 11704.00 | 580000 | 11729.00 | 581237 | 11754.00 | 582474 | 11779.00 | 583711 | 11804.00 | 584948 | 11829.00 | 586185 | 1185 |



































































