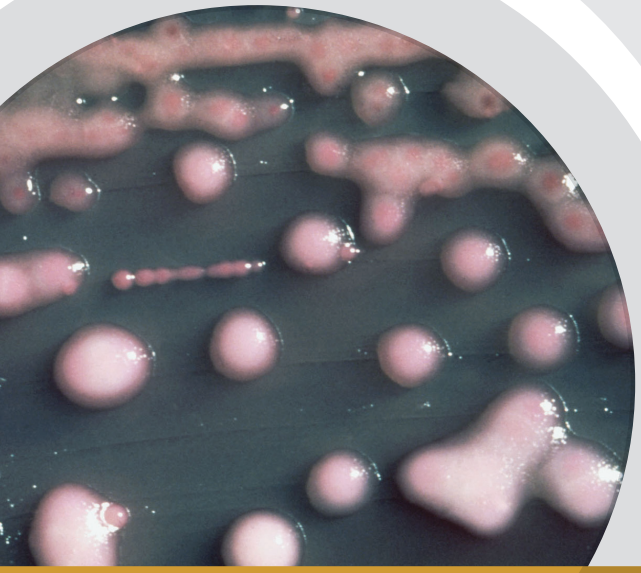

TECHNICAL REPORT

Systematic review of the effectiveness of infection control measures to prevent the transmission of carbapenemase-producing Enterobacteriaceae through cross-border transfer of patients

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Systematic review of the effectiveness of infection control measures to prevent the transmission of carbapenemase-producing Enterobacteriaceae through cross-border transfer of patients

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Suggested citation: European Centre for Disease Prevention and Control. Systematic review of the effectiveness of infection control measures to prevent the transmission of carbapenemase-producing Enterobacteriaceae through cross-border transfer of patients. Stockholm: ECDC; 2014.

Stockholm, December 2014

ISBN 978-92-9193-614-4

doi 10.2900/418192

Catalogue number TQ-05-14-125-EN-N

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Abbreviations

AE	Adverse event
CI	Confidence interval
CDC	Centers for Disease Control and Prevention, United States
CLSI	Clinical Laboratory Standards Institute
CNSE	Carbapenem-non-susceptible Enterobacteriaceae
CPE	Carbapenemase-producing Enterobacteriaceae
CPGN	Carbapenemase-producing gram-negative bacteria
CRD	Centre for Reviews and Dissemination
CRE	Carbapenem-resistant Enterobacteriaceae
CRKP	Carbapenem-resistant *Klebsiella pneumoniae*
DARE	Database of Abstracts of Reviews of Effects
E. coli	*Escherichia coli*
EARS-Net	European Antimicrobial Resistance Surveillance Network
ECDC	European Centre for Disease Prevention and Control
ER	Emergency room
ESBL	Extended-spectrum β-lactamase
ESBL-E	Extended-spectrum β-lactamase-producing Enterobacteriaceae
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
EU/EEA	European Union and European Economic Area
EUCAST	European Committee on Antimicrobial Susceptibility Testing
GIN	Guidelines International Network
HCW	Healthcare worker
hr	Hour
HRE	Highly-resistant Enterobacteriaceae
HTA	Health Technology Assessment
ICU	Intensive care unit
KPC	*Klebsiella pneumoniae* carbapenemase
KSR Ltd	Kleijnen Systematic Reviews Ltd
LTCF	Long-term care facility
MBL	Metallo-β-lactamase
MDRO	Multidrug-resistant organism
MHT	Modified Hodge test
MICs	Minimum inhibitory concentrations
MICU	Medical intensive care unit
MRSA	Meticillin-resistant *Staphylococcus aureus*
mth	Month
N/A	Not applicable
NDM-1	New Delhi metallo-β-lactamase-1

NICU	Neonatal intensive care unit
NR	Not reported
OR	Odds ratio
ORION	Outbreak Reports and Intervention Studies of Nosocomial Infection
OXA-48	Carbapenem-hydrolyzing oxacillinase-48
PCR	Polymerase chain reaction
Pt	Patient
RCT	Randomised controlled trial
SD	Standard deviation
SICU	Surgical intensive care unit
VIM	Verona integron-encoded metallo-β-lactamase
VRE	Vancomycin-resistant *Enterococcus* spp.
WHO	World Health Organization
wk	Week
yr	Year

1 Executive summary

1.1 Background and introduction

Carbapenemase-producing Enterobacteriaceae (CPE) produce enzymes that can efficiently hydrolyse and confer resistance to most β-lactams, including the carbapenems. In addition, many CPE strains frequently carry additional genetic determinants that confer resistance to other non-β-lactam antibiotics, making these bacteria resistant to most antibiotics.

The emergence and spread of CPE is a public health threat, especially because infections caused by CPE are associated with an increase of morbidity, mortality, and healthcare costs. Curbing the spread of CPE after their importation into healthcare facilities is important, as is controlling transmission in areas where they have become endemic, because they are associated with poor patient outcomes. Identifying the effective infection control measures that can be implemented is an important step in order to prevent patients from becoming colonised or infected with these multidrug-resistant organisms (MDROs). Although some European countries have addressed the spread of CPE by creating new or modified guidelines/strategies for other MDROs or national/local task forces, few published official guidelines or guidance documents relating to infection control measures for CPE have been published.

1.2 Aims and objectives

This systematic review is an update of the previous European Centre for Disease Prevention and Control (ECDC) risk assessment from 2011 [1], which was composed of a systematic review and guidance document. The aim of the 2011 ECDC risk assessment was to identify the evidence for the effectiveness of targeted infection control measures for the containment of spread and transmission of CPE through patient transfer between healthcare facilities, with a special emphasis on cross-border transfer. The goal of this systematic review is to update the 2011 risk assessment and the evidence from this will be used to develop guidance, which can be used by countries in the European Union and the European Economic Area to help curb the spread of CPE.

1.3 Methods

All stages of the review process adhered to published systematic review methods as recommended in the Cochrane Handbook [2] and the Centre for Reviews and Dissemination (CRD) guidance [3] for carrying out systematic reviews. This review reports data only for studies published since August 2010, the end of the literature search for the 2011 ECDC systematic review. The findings from this review are briefly summarised. New findings and conclusions from this review, as well as the conclusions from the 2011 ECDC review, are reported.

All studies, regardless of design, were selected for inclusion if they evaluated an infection control intervention for patients who were admitted or transferred to healthcare facilities and who were at risk of becoming colonised or infected with CPE. Relevant outcomes were the transmission or spread of CPE within a healthcare facility. Items 9 and 17 from the 'Outbreak reports and intervention studies of nosocomial infection' (ORION) statement [4] were used for inclusion of studies.

Searches were not restricted by study design, language or publication status. Six electronic resources were searched from 10 July 2013 to 17 July 2013, including MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database (HTA) and the International Network of Agencies for Health Technology Assessment (INAHTA) databases and bibliographies of identified research and review articles were also checked for further studies.

All stages of the review process involved at least two reviewers working independently, and disagreement was resolved through discussion and checking by a third reviewer.

Quality assessment was carried out using the criteria of Downs & Black, or, if studies were comparative (i.e. had two study arms each with a different intervention), the criteria developed by the Cochrane Collaboration.

Statistical pooling of the data using meta-analyses was not performed due to the heterogeneous nature of the studies and a narrative synthesis of the studies was reported.

The evidence which supported the various infection control measures was reported using the evidence levels described by The Grading of Recommendations Assessment, Development and Evaluation Working Group [5] with evidence from observational studies graded as '++'.

1.4 Results

A limited number (n=6) of observational studies were included. No controlled study was identified, and all studies used a quasi-experimental/before-and-after design. Most studies (n=5) were from CPE-endemic areas, Israel (n=4) and Greece (n=1), and four were outbreak reports in adult populations in acute healthcare settings. The overall quality of the six studies included in the analysis was moderate at best.

All six studies described multi-faceted interventions. Overall, the effectiveness of individual infection control measures was difficult to interpret because they were mostly implemented as part of multi-faceted bundles (either simultaneously or in phases), compliance was variably reported, and the quality of the limited number of studies was moderate at best.

The low-grade evidence from the small number of included studies supports the effectiveness of the following infection control measures: contact precautions, patient cohorting, dedicated nursing or other types of dedicated care by staff members, hand hygiene, patient isolation, nursing (or staff) cohorting, environmental cleaning, active screening on admission to specific ward/unit, active surveillance during an outbreak, active screening on admission to hospital, staff education, case notification/flagging, contact tracing, pre-emptive isolation, and antibiotic restriction.

1.5 Discussion

This systematic review sought to provide an update on the best available evidence for interventions to control the transmission and spread of CPE through patient transfer between healthcare facilities, with special emphasis on cross-border transfer. The strengths of the review include adherence to accepted rigorous standards for the conduct of systematic reviews, the close involvement and advice of a topic expert from ECDC, and the use of extensive literature searches to identify relevant data. The review synthesis was limited to studies considered to represent the best available evidence.

Multiple factors limited the strength of the findings, including the substantial risk of bias associated with the lack of good quality studies, the inclusion of poor reporting, the lack of single intervention studies and variable compliance reporting and the magnitude of effects associated with the interventions. Therefore only limited conclusions can be drawn from this evidence and as such they should be considered as suggestive of further research.

1.6 Conclusions

- As stated in the 2011 ECDC risk assessment, there is no evidence of infection control measures to specifically prevent the transmission of CPE during cross-border transfer. Two studies included in this updated review (2013) included patients transferred between hospitals in the same region. From these studies, there is evidence that infection control measures were effective in reducing imported CPE.
- The findings from this updated review confirm and extend the findings from the 2011 ECDC risk assessment in that the evidence for the effectiveness of infection control measures comes only from observational studies reporting infection control measures in 'care bundles' (evidence level ++). This evidence is limited by the lack of data from controlled studies reporting single infection control measures.
- As in the 2011 ECDC risk assessment, evidence from outbreak reports in acute care settings was identified in this updated review for the effectiveness of the early implementation of active surveillance by rectal screening for CPE carriage on hospital admission, admission to specific wards/units, and for surveillance during outbreaks (evidence level ++).
- As in the 2011 ECDC risk assessment, evidence was identified in this 2013 review for the effectiveness of pre-emptive isolation on admission, dedicated nursing or other types of dedicated care by staff members, contact precautions (gloves and gowns) (evidence level ++).
- In this review, evidence was identified for the effectiveness of the following infection control measures: patient cohorting, hand hygiene, patient isolation, nursing (or staff) cohorting (similar to dedicated nursing), environmental cleaning, staff education, case notification/flagging, contact tracing and antibiotic restriction (evidence level ++).
- Evidence for the effectiveness of ward or ICU closure remains available from the original 2011 ECDC risk assessment. No new evidence for these was identified in this updated review.
- Other infection control measures may also be effective, but the evidence supporting their effectiveness is less clear due to a lack of data.

- The best available evidence for the effectiveness of interventions derived from this review and the 2011 ECDC risk assessment comes from data reported from observational studies which, for the most part, include interventions that are part of a bundle of measures, making the effectiveness of each measure less clear. It would, therefore, be necessary to strive for better designed and reported studies that provide evidence for the benefit and harm of infection control measures for the prevention and control of CPE.

2 Background

2.1 Classification and epidemiology

Over the past decade, carbapenemases, a group of clinically important β-lactamases have emerged and spread among Enterobacteriaceae [6]. One of the milestones in the emergence of carbapenemases in Enterobacteriaceae was the detection of a novel carbapenemase, *Klebsiella pneumoniae* carbapenemase (KPC), in a *Klebsiella pneumoniae* isolate in North Carolina, USA, which later successfully spread throughout the world [6]. Since then, most acquired carbapenemases have been found and reported in carbapenemase-producing Enterobacteriaceae (CPE) globally [7,8]. Carbapenemases are enzymes that can efficiently hydrolyse most β-lactams, including carbapenems [9,10]. In addition, many CPE strains frequently carry additional resistance determinants to other non-β-lactam antibiotics, making these organisms resistant to most antimicrobials. CPE commonly remain susceptible to only a few classes of antimicrobials, usually the polymyxins, tigecycline, fosfomycin, and nitrofurantoin. There is no proven clinical efficacy against these strains, and in fact there are reports of clinical failures [11] and emerging resistance to these remaining antimicrobials [12-15].

The emergence and spread of CPE has also been identified as a public health threat, especially since studies on CPE [16,17] and carbapenem-non-susceptible Enterobacteriaceae (CNSE) [18,19] have shown that infection or colonisation has been associated with higher in-hospital mortality. Similarly, outcome studies involving patients infected with MDROs show that an inadequate choice or the delayed administration of antimicrobial therapy is associated with poorer patient outcomes, increased morbidity, mortality, increased length of hospital stay and increased costs [20-25]. The risk to patients infected with these MDROs becomes even greater, given the very limited number of new antimicrobial agents that are in the developmental pipeline [26,27].

2.2 Worldwide spread

In the last decade, there has been a rapid increase of CPE and CNSE worldwide [28].

All carbapenemases have been described as members of the Enterobacteriaceae family, including *E. coli*, *K. pneumoniae*, *Serratia marcescens*, *Citrobacter* spp., and *Enterobacter* spp., and interspecies spread has also been reported, perhaps demonstrating the facility with which the genetic elements can disseminate [29-33].

In Europe, antimicrobial susceptibility testing data and trends for *K. pneumoniae* resistance to carbapenem antimicrobials have been reported annually since 2005 through the European Antimicrobial Resistance Surveillance Network (EARS-Net, formerly EARSS). In the EU/EEA, data on antimicrobial resistance from EARS-Net from 2013 [34] demonstrated that, while in most European countries rates of carbapenem resistance in invasive *K. pneumoniae* isolates from blood and cerebrospinal fluid were below 1%, the population-weighted mean showed a significantly increasing trend from 4.6% in 2010 to 8.3% in 2013. This increase in *K. pneumoniae* resistance to carbapenems has been confirmed by a previous trend analysis of resistance [34] by ECDC [35] and a recent online survey performed as part of the ECDC-funded European Survey on CPE (EuSCAPE) [36]. This demonstrates that CPE are spreading in Europe and strongly suggests that these data may only represent the tip of the iceberg.

The dissemination of these mobile genetic elements (e.g. transposon and plasmids) and of epidemic strains occurs through human population mobility and, more specifically, through patient transfer between healthcare facilities, not only within the same country but also across borders [37-40]. In fact, the first epidemiological evidence of intercontinental spread of KPC-producing *Klebsiella pneumoniae* was described in reports from France [41] and Israel [38] after it was detected following introduction from the USA. Since then, many other reports have documented cross-border importation between healthcare facilities resulting from patient transfer, not only within Europe but also from outside European borders. Secondary transmission of these organisms has been reported, leading to outbreaks, epidemics, and in some countries endemicity [8,42,43] [28,36,44-47].

2.3 Issues in laboratory detection

Detecting carbapenemases can be particularly challenging for a number of reasons, which range from clinical and infection control to laboratory issues. Clinical or infection control issues can include lack of hospital or national infection control protocols that suggest active screening, incomplete evaluation which patients should be actively screened or cultured, and resource-poor settings where implementation of infection control measures is difficult once detection of carbapenemases is suspected or confirmed.

In order to implement infection control in a timely manner, but also for therapeutic purposes, it is important that local microbiology laboratories should be able to detect carbapenem resistance in a timely manner and with high sensitivity at the point of care. Similarly, it is important for local and/or reference laboratories to be able to quickly confirm the presence of carbapenemases in Enterobacteriaceae [48-51]. As previously stated, carbapenemases are

enzymes that can efficiently hydrolyse most β-lactams, including carbapenems [9,10]. One of the main reasons that timely detection can be challenging in the laboratory is that not all carbapenemases will confer clinical carbapenem resistance, and this is particularly true for the Enterobacteriaceae. The definition of a carbapenemase therefore relies not on the ability to confer clinical resistance to carbapenems but on the hydrolytic capacity of carbapenems measured by quantitative spectrophotometry. Based on this definition, detection of the genes encoding the enzymes regarded as carbapenemases is usually an appropriate confirmation of carbapenemase production.

However, detection of either carbapenem resistance or the presence of carbapenemases can be compromised by various diagnostic difficulties. CPE can demonstrate significant variation in their carbapenem minimum inhibitory concentrations (MICs), even falling within the susceptibility range defined by either the Clinical Laboratory Standards Institute (CLSI) [52] or the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [53]. Breakpoints for carbapenem susceptibility among Enterobacteriaceae have been proposed both by EUCAST [53] and CLSI, although prior to 2010 the ones proposed by EUCAST were lower than CLSI's. In 2010, however, the CLSI revised their proposed breakpoints and lowered them in an effort to better detect resistant to carbapenems [54]. The diagnostic accuracy for the detection of carbapenem resistance and the presence of a carbapenemase can be affected by a number of factors, including the bacterial species being tested; the class of carbapenemase produced by the organism [55,56]; the geographical origin of the bacterial species; heteroresistance [57] and the presence of other resistance mechanisms, such as ESBLs, porin mutations and/or presence of efflux pumps [58-61]. Furthermore, certain testing methods, such as automatic testing, have been shown to not always distinguish between Enterobacteriaceae that produce carbapenemases and those carrying other mechanisms of resistance (e.g. ESBLs and/or porin loss) [60,62]. Difficulties also exist when using automated diagnostic testing systems to detect specific carbapenemases, e.g. OXA-48, because these isolates can remain susceptible to extended-spectrum cephalosporins and monobactams, but resistant to carbapenems [62,63]. They may also have lower MICs to carbapenem antimicrobials and may therefore not be detected.

Recently, phenotypic tests have become available that correlate well with the presence of clinically important carbapenemases. However, false positive and false negative results have been reported, especially when using the Modified Hodge Test (MHT), and therefore caution should be exercised in interpreting results [64,65]. False detection (false positive MHT) of a carbapenemase can occur because of the presence of other resistance mechanisms, e.g. ESBLs and/or porin loss [64]. False negative results of the MHT have also been recently reported when testing NDM-1-producing bacterial strains [65].

In order to identify isolates with specific types of carbapenemase production more accurately, other screening methods have been proposed and validated. Examples of these are disk diffusion synergy tests, using carbapenemase-inhibiting compounds such as boronic acid for KPC and dipicolinic acid for MBL [55,60,66-68]. The use of selective chromogenic agar media has also been proposed for rapid screening purposes [63,69,70]. Finally, molecular confirmation tests, such as the single or multiplex PCR, which are usually limited to use in reference laboratories or under epidemic conditions, have also been evaluated and have shown good results [71,72].

2.4 Issues in infection control

CPE can colonise or infect not only those patients who are debilitated, immunocompromised or critically ill, but also those who were previously healthy and became colonised or infected in healthcare settings practicing poor infection control. This poses an obvious threat to patient safety since infection with these MDROs is associated with worse outcomes, prolonged hospitalisation and higher mortality rates [17,18,73].

It is necessary to prevent the spread of CPE in healthcare facilities immediately after their importation and reduce their spread when they have already become endemic in a healthcare system. Knowing which infection control measures are effective and should be implemented is of paramount importance. Because of the difficulty in assessing the effectiveness of these measures, the ORION statement [4] was developed as a standard for the transparent reporting of infection control interventions during outbreaks.

2.5 Guidelines and guidance relating to infection control measures

In response to the growing threat of CPE spread in healthcare systems, various guidance documents and toolkits have been published by societies, public health agencies and scientific groups, providing recommendations for the implementation of multimodal infection control interventions to prevent the spread of CPE in acute healthcare facilities. Examples of these key documents are those that have been published by ECDC (2011 risk assessment on CPE) [1], the United States Centers for Disease Control and Prevention (CDC) [74], Carmeli 2010 [40], Schwaber 2011 [50], Parker et al. (Agency for Healthcare Research and Quality) [75] and Tacconelli 2014 [76].

In addition, some countries in Europe and beyond, have addressed the spread of CPE by creating new or modified guidelines or strategies or by creating national task forces for CPE and/or other MDROs [50] in order to tackle this public health threat (see Table 1). Examples of these documents for MDROs, which also feature sections on CPE/CRE, include the Irish Health Protection Surveillance Centre (HPSC) [77]; the French Haut Conseil de la Santé Publique [78,79]; and Public Health England in 2013 [80]. Guidance documents have also been published by certain countries, specifically on the prevention of MDROs with cross-border transfer of patients [168]. Following communication from EU Member States, the 2011 ECDC report [1] included a formative table of guidelines/guidance from different countries. ECDC also published an online directly which contains a compilation of all currently available guidance documents for the prevention and control of carbapenemase-resistant Enterobacteriaceae [169].

3 Objectives

In 2011, ECDC published a technical report presenting the results of two systematic reviews, entitled 'Risk assessment on the spread of carbapenemase-producing Enterobacteriaceae (CPE) through patient transfer between healthcare facilities, with special emphasis on cross-border transfer' [1]. This risk assessment was published to provide evidence to countries on effective infection control measures to limit the spread of CPE.

The objective of this review is to update the systematic review performed by ECDC in 2011, to identify new (published since August 2010) evidence on the effectiveness of infection control measures to limit the spread of CPE when transferring patients to healthcare settings, especially cross-border. Given the likely lack of infection control measures published for the prevention of cross-border transfer of CPE and the spread/transmission of CPE between healthcare facilities any setting where patients could be exposed to CPE were also included.

The conclusions from this systematic review will be used to update the conclusions of the 2011 ECDC systematic review where necessary and will be reviewed by an expert group coordinated by ECDC to develop guidance. This guidance will be available to EU/EEA Member States to adapt or adopt in order to curb the spread of CPE.

4 Key points from the 2011 ECDC technical report: 'Risk assessment on the spread of carbapenemase-producing Enterobacteriaceae (CPE) through patient transfer between healthcare facilities, with special emphasis on cross-border transfer'

4.1 Goals and conclusions of the 2011 ECDC risk assessment

The 2011 ECDC risk assessment [1] is comprised of the two systematic reviews listed below:

- What are the risk factors for patient colonisation or infection with CPE?
- How effective is the use of screening, in addition to targeted infection control measures, in reducing the incidence of healthcare facility- and ICU-acquired colonisation or infection with CPE?

4.1.1 Conclusions of the ECDC 2011 systematic review on risk factors for patient colonisation or infection with CPE

- There is strong evidence that cross-border transfer of patients is associated with a risk of CPE transmission when:
  a) patients are transferred from areas with high rates of CPE to healthcare facilities in another country and
  b) patients have received medical care abroad in areas with high rates of CPE.
- There are limited data available from the studies on inter-healthcare transmission of CPE within countries, although many imported CPE isolates were responsible for secondary transmission within the healthcare facilities of the destination country.
- In order to avoid publication and ascertainment bias, it is necessary to encourage more active reporting of CPE cases associated with cross-border transfer from all countries in Europe and globally in order to have a complete epidemiological picture of the true risk of CPE spread.
- The risk factors identified for CPE spread were similar in most studies and included prior use of antimicrobials, in particular carbapenems, fluoroquinolones, cephalosporins, anti-pseudomonal penicillins and metronidazole.

4.1.2 Conclusions of the ECDC 2011 systematic review on effective infection control measures for the prevention and control of transmission of CPE[1]

- There is only limited volume and strength of evidence available to date on the effectiveness of infection control measures for the prevention and control of nosocomial transmission of CPE in acute healthcare settings and no evidence in other care settings.
- The available low-grade evidence derived from outbreaks in acute care hospitals consistently supports the effectiveness of early implementation of active surveillance by rectal screening of CPE carriage and additional precautions for care of CPE-positive patients, including wearing of disposable gloves and gown, and cohort nursing by a separate dedicated team.
- Other non-targeted infection control interventions may be of additional benefit but the evidence supporting their effectiveness is less clear due to even more limited data.
- The evidence on effective containment of secondary transmission following cross-border transmission of CPE by patient transfer between acute care facilities is unclear due to incomplete reporting of infection control management and outcome from available case series.
- There is a need for better designed and reported studies of the benefit and harm of infection control measures for the prevention and control of nosocomial transmission of CPE in acute and other care healthcare settings in endemic and non-endemic regions, including in the context of cross-border care.

[1] Reported in the 2011 ECDC risk assessment [1]

These conclusions were used to create guidance, published as part of the 2011 ECDC risk assessment [1]. The findings and conclusions from the 2011 review of infection control measures are detailed in Section 4.2.

The current 2013 update of the 2011 ECDC report again focuses on the systematic review of the effectiveness of interventions to prevent the spread and transmission of CPE but this time, does not address patient risk factors.

5 Methods used in the 2013 updated systematic review

There were differences in the methodology used in the 2011 ECDC systematic review and this 2013 update. More specifically, in this review, the literature searches were expanded from the original review to include additional relevant terms and the included, the studies were assessed using a different quality assessment tool developed by Downs & Black [93] to assess the risk of bias within observational studies. An additional difference was that in the 2013 review, studies meeting the inclusion criteria underwent an additional screening process whereby they were only included if they fulfilled items 9 and 17 (intervention description and outcome assessment, respectively) of the ORION checklist [4].

All stages of both reviews, however, were performed independently by two reviewers, with the intervention of a third reviewer where necessary in accordance with accepted systematic review methods and practice [2,3].

5.1 Inclusion criteria

This review included the following types of studies.

5.1.1 Population

Patients admitted or transferred to healthcare facilities that are at risk of becoming colonised or infected with CPE.

This included (but was not limited to) patients who were exposed to cases of CPE introduced by cross-border transfer. Also included was the introduction of CPE into non-endemic or endemic healthcare facilities and countries, where patients could be exposed.

'Healthcare facilities' included the following: secondary and tertiary healthcare facilities, acute care facilities, hospitals, intensive care units (ICUs), long-term care facilities (LTCFs), nursing homes, rehabilitation centres and step-down units.

5.1.2 Interventions and comparators

Targeted or non-targeted infection control interventions, as compared to using only standard precautions or only active patient screening. These included:

Screening: Active surveillance cultures, active screening tests, or contact screening of at-risk patients for the detection of colonisation with 'CPE'. The sites of screening included the rectum, active wounds, and other relevant superficial body sites. Timing of screening included 'on admission', 'on discharge', in the ICU, daily or weekly or in serial point-prevalence surveys.

Additional (to standard precautions) targeted infection control precautions: Precautions restricted to the care of patients colonised or infected with CPE, patient cohorting, i.e. physical separation and/or nursing team separation for colonised and non-colonised patients, barrier precautions, barrier nursing, contact isolation, contact precautions, use of gloves, gowns and face masks.

Other infection control interventions: Pre-emptive patient isolation and contact precautions for patients at high-risk for colonisation with CPE, contact precautions for all patient care, ward closure, environmental cleaning and disinfection, antibiotic restriction or antibiotic class shift.

5.1.3 Outcome measures

Relevant outcomes were the transmission or spread of CPE within a healthcare facility, measured by the frequency or incidence of acquisition of colonisation and/or infection with these organisms.

Studies where no data on acquisition outcomes are reported were excluded.

5.1.4 Types of studies

There were no limits with regard to study type except that the study had to be a primary study.

However, the analysis was limited to those studies which reported sufficient information to meet the ORION statement for items 9 and 17 (intervention description and outcome assessment, respectively) [4]. Details of the ORION statement are given in Table 1.

5.2 Literature searches

Search strategies were developed specifically for each database and the keywords associated with the drug-resistant organisms of interest were adapted according to the appropriate syntax and configuration of each database.

Candidate search terms were identified from target, browsing database thesauri (e.g. MEDLINE MeSH and EMBASE Emtree) and initial scoping searches. These scoping searches and the existing 2011 ECDC technical review [1] were used to generate test sets of target references, which informed the text mining analysis of high-frequency subject indexing terms using EndNote reference management software. Strategy development involved an iterative approach testing candidate text and indexing terms across a sample of bibliographic databases, aiming to reach a satisfactory balance of sensitivity and specificity.

Searches were not restricted by study design, in order to ensure that both quantitative and qualitative evidence was identified. No restrictions on language or publication status were applied, and limits were not applied to exclude animal studies.

In order to meet the objective of this project, a focussed, updated search based on search terms from the original ECDC report [1] was undertaken to identify evidence published since the last searches were completed in August 2010. In order to maximise sensitivity while balancing specificity, the update strategy drew on terminology from the original search, but also included additional terminology identified from relevant references included in the 2011 report [1].

Table 1: Summary of reporting standards for transparent reporting of outbreak reports and intervention studies of nosocomial infection (ORION statement)

Item	Item Number	Description of item
Title and Abstract	1	Description of paper as outbreak report or intervention study. Design of intervention study (e.g. randomised controlled trial, cluster randomised controlled trial, interrupted time series, cohort study, etc.). Brief description of intervention and main outcomes.
Introduction Background	2	Scientific and/or local clinical background and rationale. Description of organism as epidemic, endemic or epidemic becoming endemic.
Type of paper	3	Description of paper as intervention study or an outbreak report. If an outbreak report, report the number of outbreaks.
Dates	4	Start and finish dates of the study or report.
Objectives	5	Objectives for outbreak reports. Hypotheses for intervention studies
Methods Design	6	Study design. Use of EPOC classification recommended (RCT, NRCT, CBA or ITS) Whether study was retrospective, prospective or ambidirectional. Whether decision to report or intervene was prompted by any outcome data. Whether study was formally implemented with predefined protocol and endpoints.
Participants	7	Number of patients admitted in study or outbreak. Summaries of distributions of age and lengths of stays. If possible, proportion admitted from other wards, hospitals, nursing homes or from abroad. Where relevant, potential risk factors for acquiring the organism. Eligibility criteria for study. Case definitions for outbreak report.
Setting	8	Description of the unit, ward or hospital and, if a hospital, the units included. Number of beds, the presence and staffing levels of an infection control team.
Interventions	9	Definition of phases by major change in specific infection control practice (with start and stop dates). A summary table is strongly recommended with precise details of interventions, how and when administered in each phase.
Culturing and typing	10	Details of culture media, use of selective antibiotics and local and/or reference typing. Where relevant, details of environmental sampling.

Item	Item Number	Description of item
Infection-related outcomes	11	Clearly defined primary and secondary outcomes (e.g. incidence of infection, colonisation, bacteraemia) at regular time intervals (e.g. daily, weekly, monthly) rather than as totals for each phase, with at least three data points per phase and, for many two phase studies, 12 or more monthly data points per phase. Denominators (e.g. numbers admissions or discharges, patient bed days). If possible, prevalence of organism and incidence of colonisation on admission at the same time intervals. Criteria for infection, colonisation on admission and directly attributable mortality. For short studies or outbreak reports, use of charts with 'duration patient stay' and 'date/s organism detected' may be useful (see text).
Economic outcomes	12	If formal economic study done, definition of outcomes to be reported, description of resources used in interventions, with costs broken down to basic units, stating important assumptions.
Potential threats to internal validity	13	Which potential confounders were considered, recorded or adjusted for (e.g. changes in length of stay, case mix, bed occupancy, staffing levels, hand-hygiene compliance, antibiotic use, strain type, processing of isolates, seasonality). Description of measures to avoid bias including blinding and standardisation of outcome assessment and provision of care.
Sample size	14	Details of power calculations, where appropriate
Statistical methods	15	Description of statistical methods to compare groups or phases. Methods for any subgroup or adjusted analyses, distinguishing between planned and unplanned (exploratory) analysis. Unless outcomes are independent, statistical approaches able to account for dependencies in the outcome data should be used, adjusting, where necessary, for potential confounders. For outbreak reports statistical analysis may be inappropriate.
Results Recruitment	16	For relevant designs: dates defining periods of recruitment and follow-up. A flow diagram is recommended to describe participant flow in each stage of study.
Outcomes and estimation	17	For the main outcomes, the estimated effect size and its precision (usually using confidence intervals). A graphical summary of the outcome data is often appropriate for dependent data (such as most time series).
Ancillary analyses	18	Any subgroup analyses should be reported and it should be stated whether or not it was planned (specified in the protocol); possible confounders should be adjusted for.
Adverse events	19	Pre-specified categories of adverse events and occurrences of these in each intervention group. This might include drug side effects, crude or disease-specific mortality in antibiotic policy studies or opportunity costs in isolation studies.
Discussion Interpretation	20	For intervention studies: assessment of evidence for/against hypotheses, accounting for potential threats to validity of inference including regression to mean effects and reporting bias. For outbreak reports, consider clinical significance of observations and hypotheses generated to explain them.
Generalisability	21	External validity of the findings of the intervention study, i.e. to what degree can results be used to draw general inferences about different target populations or settings.
Overall evidence	22	General interpretation of results in context of current evidence.

Abbreviations: RCT: randomised controlled trial; CRCT: cluster randomised controlled trial; CBA: controlled before and after study ITS: interrupted time series

As reported in: http://www.idrn.org/orion.php

The following databases were searched as an update with the date limit August 2010 to July 2013:

- MEDLINE (OvidSP): 2010/08-2013/07/wk 1
- MEDLINE In-Process Citations and Daily Update (OvidSP): up to 15 July 2013
- EMBASE (OvidSP): August 2010–15 July 2013
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): 2010–June 2013, Issue 6
- Health Technology Assessment Database (HTA) (Wiley): 2010–2013/Issue 2
- International Network of Agencies for Health Technology Assessment (INAHTA) Publication (internet): 2010–16 July 2013

Full details of the search strategies are reported in Appendix 1.

5.2.1 Reference checking

The bibliographies of identified research and review articles were checked for studies.

5.2.2 Handling of citations

Identified references were imported into EndNote X4 and de-duplicated.

5.2.3 Quality assurance within the search process

For all searches undertaken by the Kleijnen Systematic Reviews information team, the main EMBASE strategy for each set of searches was independently peer reviewed by a second information specialist, using the PRESS-EBC checklist [94,95].

5.3 Methods of study selection, quality assessment and data extraction

5.3.1 Study selection

Two reviewers independently inspected the abstract/title of each identified reference and determined its potential relevance to the review. For potentially relevant articles, or in cases of disagreement, the full article was obtained and assessed in detail. Any disagreement was resolved through discussion and checked by a third reviewer. Justification for excluding studies was documented (see Appendix 3).

5.3.2 Assessment of methodological quality (risk of bias)

Quality assessment was only carried out for those studies which met the inclusion criteria for the review and also met the ORION statement for items 9 and 17 (intervention description and outcome assessment, respectively) [4].

The methodological quality (risk of bias) of the studies was assessed independently by two reviewers using the criteria of Downs & Black (see Appendix 2 for further details) [93]. Any disagreements were resolved by consensus and checked by a third reviewer. The results of the quality assessment were presented to provide an evaluation of the overall quality of the evidence and to provide a transparent method of recommendation for the design of future studies.

5.3.3 Data collection

Data extraction sheets were individually designed and piloted using Microsoft Excel 2007. For each study meeting the review inclusion criteria, the following information was recorded: study ID, country/region; study aim; bacterial type; intervention details; study design; sample size; and outcomes reported.

For those studies which also met the ORION statement for items 9 and 17 and which were to be included in the synthesis, further details were extracted. These included details of the population, assessment methods, statistical analysis methods, outcome data and study conclusions. Further details can be found in Appendix 5.

Studies were identified by the main study name/identifier. If not available, the surname of the first author of the main report/publication was used, followed by the year of publication. To avoid the duplication of data where studies (or study populations) had multiple publications, the most recent and complete report was used as the main reference, but additional details were extracted from the other publications as necessary.

Data extraction was carried out by two reviewers. Any disagreements were resolved by checking the original paper and reaching consensus, otherwise a third reviewer was asked to resolve any outstanding discrepancy.

5.4 Data synthesis

Data synthesis centred on the studies which met the inclusion criteria, and also reported sufficient details of the intervention used and the outcome data recorded (meeting items 9 and 17 of the ORION statement) [4]. Those studies which did not meet the required ORION criteria were summarised in tables (Appendix 7), but not discussed further in the review.

A narrative summary of the studies included in the data synthesis is presented. This includes a summary of the characteristics (e.g. study designs, population sizes, geographical location, year, baseline population characteristics, interventions, and outcome definitions etc.) and methodological quality of the studies. Factors which may introduce bias or limit the generalisability of the findings were identified and discussed. The data were summarised using text and, where relevant, accompanying tables and figures.

Given the heterogeneous nature of the study designs, populations (e.g. type of infections, interventions, age, gender, ethnicity, geographical location) and methods (e.g. outcome definitions and assessment methods), statistical pooling of the data using meta-analyses was not possible.

The evidence to support each of the individual infection control measures was described using the evidence levels described by The Grading of Recommendations Assessment, Development and Evaluation Working Group (GRADE) [5] with evidence from observational studies graded as '++'.

6 Results from the updated review (2013) of the effectiveness of infection control interventions

6.1 Literature searches and inclusion assessment

In total, 3 277 records (after de-duplication in EndNote) were retrieved from six electronic databases. The titles (and where available, abstracts) for each record were each screened by two independent reviewers for potential relevance to each of the review questions. From these records, 113 full-text articles were ordered (112 were obtained) and screened in detail again by two independent reviewers to determine whether they fulfilled the review inclusion criteria. In addition, we found an additional relevant poster linked to a paper, giving a total of 113 full-text articles to screen.

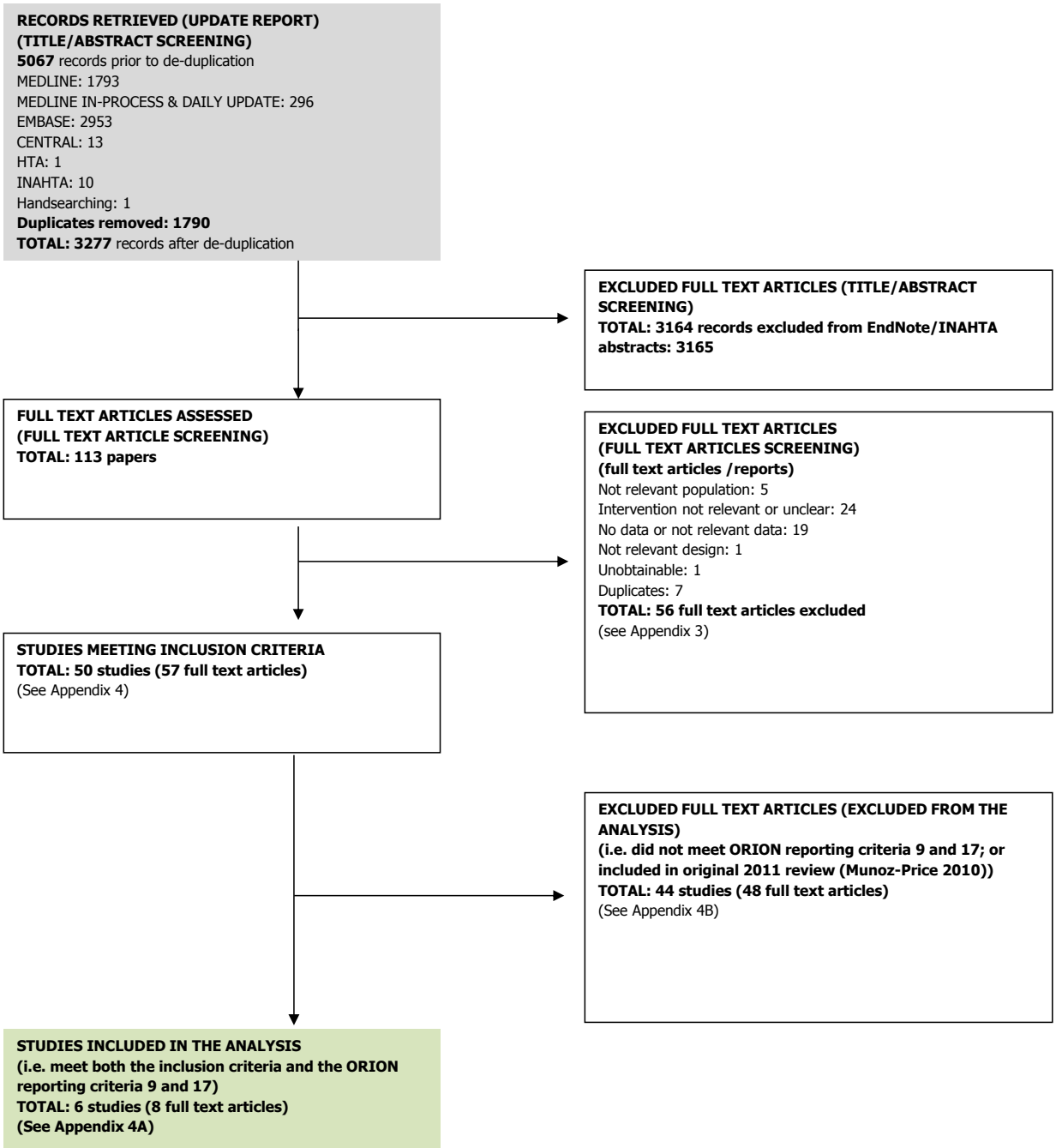
A total of 56 full-text articles were subsequently excluded for the following reasons: (a) five did not report a relevant population, (b) in 24 full-text articles the intervention was either irrelevant or unclear, (c) in 19 full-text articles there were no data or irrelevant results data, and (d) seven full-text articles were duplicates. One scientific poster was identified during data extraction linked to a full paper. One full paper could not be accessed despite repeated efforts and therefore were classified as 'unobtainable'. Further details of the excluded trials are reported in Appendix 3.

A total of 57 full-text articles (comprising 50 separate studies) were selected which met the inclusion criteria. Further details of these full-text articles are reported in Appendix 4.

After reviewing the included full-text articles it was found that many of these failed to provide sufficient details of how and when the infection control measures were applied. In addition, many took the form of an outbreak description and merely described individual cases from an outbreak or the number of cases that developed from an index case, reporting that all cases were resolved after appropriate measures were taken. Given that only limited evidence could be derived from these studies, the analysis of this report focuses on those studies which report adequate details on infection control measures and their execution and gave data which could be analysed in a meaningful way. Hence, only studies meeting the ORION reporting criteria for items 9 and 17 [4] (seven studies reported in eight full-text articles) were chosen (see Appendix 4A). However, one of the studies (Munoz-Price 2011 [84] was included in the previous 2011 ECDC risk assessment and was therefore not included in the analysis although it did meet the ORION reporting criteria for items 9 and 17.

All the studies meeting the inclusion criteria, but not included in the analysis (44 studies reported in 48 full-text articles) are summarised in Appendix 4B. This list of studies also includes one study (Munoz-Price 2010 [84]) which did meet the ORION reporting criteria for items 9 and 17 [4] but was included in the previous 2011 ECDC risk assessment [1]. To avoid the duplication of data, this was not included in this updated review.

Figure 1: Summary of study flow and selection



6.2 Overview of included studies

6.2.1 Study characteristics

Fifty studies were judged to have met the inclusion criteria for the review. After further assessment using items 9 and 17 of the ORION statement [4], six studies were judged to have reported sufficient detail and to represent the best available evidence for the assessment of effectiveness; they are summarised below and in Appendix 5. The 44 studies (reported in 49 publications) which met the inclusion criteria, but which were subsequently excluded from the main synthesis, are presented in Appendices 4B and 7.

Chitnis 2012 [96], Ciobotaro 2011 [97], Cohen 2011 [98], Poulou 2012 [99] and Schwaber 2014 [50,100]) were all single-arm studies. Three of the studies used bundles of interventions where components were added sequentially and data reported for each of the different stages. Poulou 2012 [99] incorporated infection control measures in a three-stage process over a three-year period, while both Chitnis 2012 [96] and Cohen 2011 [98] used a four-phase

implementation. Chitnis 2012 [96] introduced components at different stages over an 18-month period, while Cohen 2011 [98] used a stepwise approach with four stages over a 43-month time period. Four of the studies were considered to be ambidirectional in that they prospectively followed the effects of the measures, but retrospectively identified pre-intervention infection levels (Borer 2011 [101], Chitnis 2012 [96], Ciobotaro 2011 [97] and Schwaber 2014 [50,100]). Only two studies appeared to gather data prospectively (Cohen 2011 [98] and Poulou 2012 [99]).

The populations under study varied between studies, and the total sample of patients at risk of infection was often not clearly reported. Some studies reported the total number of beds/patients in the units or the total number of patients eligible to be screened – the maximum number being a sample of >335 000 patients, 603 of whom were positive for CPE (Cohen 2011 [97]). Two studies only reported the number of cases and not the numbers of patients admitted and eligible for screening (Chitnis 2012 [96] :99 cases, Poulou 2012 [99]: 73 cases). All studies reported that these data were gathered at various time points between the beginning of 2005 to the end of 2011. The earliest time point for recorded data was 2005 (Schwaber 2014 [50,100]).

Only one study – carried out in Greece (Poulou 2012 [99]) – was based in Europe. Four studies were based in the Middle East, all in Israel (Borer 2011 [101], Ciobotaro 2011 [97], Cohen 2011 [98], and Schwaber 2014 [50,100]). The one remaining study was carried out in the USA (Chitnis 2012 [96]). The studies from Israel and Greece described the study region as endemic for CPE. The remaining study region in the USA was described as non-endemic (Chitnis 2012 [96]). Four studies reported outbreaks of CPE/CRE (Borer 2011 [101], Chitnis 2012 [96], Ciobotaro 2011 [97], and Cohen 2011 [98]), while the remaining two studies described patients affected by CPE/CRE in endemic regions but not during an outbreak (Poulou 2012 [99] , Schwaber 2014 [50,100]).

All studies but the US one, which described the setting as a long-term care facility (Chitnis 2012 [96]), were set in acute care hospitals. One study from Israel included nationwide data from 27 hospitals (Schwaber 2014 [50] [100]). Three studies included patients from the entire hospital (Borer 2012 [101], Ciobotaro 2011 [97], Cohen 2011 [98]), while the two remaining studies focussed on one or more specific wards or units. These included ICUs and other medical or surgical units/wards (Chitnis 2012 [96], Poulou 2012 [99]).

In many cases the studies contained little description of the study populations and often lacked basic details such as age, gender, ethnicity and morbidities. All studies appeared to be in adult populations. Only two studies gave specific descriptive details regarding the populations of interest (Borer 2011 [101], Chitnis 2012 [96]). The median ages of these populations were 75 years (range 43–88 years) (Chitnis 2012 [96]) and 78 years (range 18–105 years) (Borer 2011 [101]). The proportion of male patients, where reported, ranged from 38% (Chitnis 2012 [96]) to 51% (Borer 2011 [101]). Only one study gave details of the ethnicity of the included patients (Chitnis 2012 [96]). This study reported that 64% were of 'white' ethnic origin.

The included studies all aimed to evaluate the impact of an infection control measure. The majority also specifically identified the control of CPE/CRE as an objective. All six studies reported assessing multi-faceted bundles of infection control measures (details are given in Table 2).

Two studies assessed the spread and transmission of CRKP (Borer 2011 [101], Cohen 2011 [98]). One study (Poulou 2012 [99]) reported the assessment of CRE levels by including KPC-2 and VIM-1 producing *K. pneumoniae*, and another study CRKP levels (Ciobotaro 2011 [97]), which also included KPC-3 enzymes. The remaining two studies described CRE including *K. pneumoniae*, *Enterobacter aerogenes*, and other *Enterobacter* spp. (Chitnis 2012 [96]), and CRE including *Klebsiella* spp., *Enterobacter* spp., *E. coli*, and *Proteus* spp. (Schwaber 2014 [50,100]).

Methods used in the detection of CPE were reported variously. Three studies failed to clearly report the laboratory methods used (Chitnis 2012 [96], Cohen 2011 [98] and Schwaber 2014 [50,100]) although Chitnis 2012 [96] reported carrying out testing according to the 2008 Clinical Laboratory Standards Institute (CLSI) guidelines. The other three studies reported using multiple methods (Borer 2012 [101], Ciobotaro 2011 [97] and Poulou 2012 [99]). The reported methods included the E-test (Borer 2011 [101] and Poulou 2012 [99]), disk diffusion (Borer 2011 [101]), Hodge test (Borer 2011 [101]), and Microscan Walkaway (Poulou 2012 [99,101]. Four studies clearly reported using breakpoints and identified which specific breakpoints were used. These were: CLSI M100-S16 [101], CLSI M100-S18 (Chitnis 2012 [96], CLSI M100-S19 (Ciobotaro 2011 [97]), and CLSI M100-S20 (Poulou 2012 [99]).

The source of the CPE/CRE infection and colonisation was not always clearly reported and neither was any involvement of patients transferred across geographical borders. Where information was available, it appeared that the infections arose through the transfer of patients within borders (i.e. region/area to region/area) (Borer 2011 [101], Chitnis 2012 [96], Cohen 2011 [98], Poulou 2012 [99]). Similarly, it was often difficult to identify the type of healthcare setting from which the initial infection source had come from, but when reported it appeared to involve the transfer of patients from one hospital to another, transfer from the community to the hospital, spread within the hospital (Borer 2011 [101], Chitnis 2012 [96], Ciobotaro 2011 [97], Poulou 2012 [99]) and/or between wards/units within the same hospital (Chitnis 2012 [96] and Poulou 2012 [99]). Only two studies clearly identified cases having come from patients who had been at some point hospitalised in nearby hospitals (Chitnis 2012 [96],

Poulou 2012 [99]). In one study (Chitnis 2012 [96]) in a US LTCF, 16 of the cases were identified as having been transferred from seven different acute care hospitals in the surrounding area, with one acute care hospital accounting for 44% of the cases; the majority were CRKP, with the exception of one case of *E. coli* infection. In another study (Poulou 2012 [99]), medical histories revealed that some patients with community onset infections had been hospitalised over the preceding three months in various tertiary-care hospitals in Greece, and that these cases could therefore be considered as hospital-to-hospital spread.

All six studies concluded that the assessed infection control measures were effective in controlling or decreasing the spread and prevalence of CPR/CRE by the end of the study periods. The interventions (implemented in bundles) used in the six studies (Borer 2011 [101], Chitnis 2012 [96], Ciobotaro 2011 [97], Cohen 2011 [98], Poulou 2012 [99], Schwaber 2014 [50,100]) included patient cohorting, hand hygiene, and contact precautions in addition to various other measures (see Table 5). Other common interventions were patient isolation (Borer 2011 [101], Ciobotaro 2011 [97], Cohen 2011 [98], Poulou 2012 [99], Schwaber 2014 [50,100]) and the use of dedicated nursing and other staff to look after the affected patients (Borer 2011 [101], Chitnis 2012 [96], Ciobotaro 2011 [97], Cohen 2011 [98], Poulou 2012 [99] , Schwaber 2014 [50,100]).

Further details on these studies are described below and in Appendix 5.

Table 2: Summary of components included in studies of multi-faceted interventions

Study reference (first author, year)	Active screening on admission to hospital	Active screening on admission to specific ward/unit	Pre-emptive isolation of patients on admission	Contact tracing	Active surveillance during the outbreak	Patient cohorting	Patient isolation	Nursing (or staff) cohorting	Dedicated nursing or other types of dedicated care by staff members	Bathing in anti-septic	Contact pre-cautions	Hand hygiene	Ward closure	Hospital closure	Patient record flagging	Other[2]	Further details
Borer 2011	✓	✓	✓	✓	✓	✓	✓	x	✓	x	✓	✓	x	x	✓	✓	
Chitnis 2012 [96] (Staged four-phase intervention)	✓	✓	x	x	✓	x	x	x	x	x	✓	✓	x	x	x	✓	Other infection control measures: urine and sputum surveillance.
	✓	✓	x	x	✓	✓	x	✓	x	x	✓	✓	x	x	x	✓	
	✓	✓	x	x	✓	✓	x	✓	✓	x	✓	✓	x	x	x	✓	
	✓	✓	x	x	✓	✓	x	✓	✓	x	✓	✓	x	x	x	✓	
Ciobotaro 2011 [97]	✓	✓	x	x	✓	✓	✓	x	✓	x	✓	✓	x	x	✓	✓	
Cohen 2011 [98] (Staged four-phase intervention)	x	x	x	x	x	x	✓	x	x	x	✓	x	x	x	x	x	Mar 2006: Single-room isolation and contact precautions
	x	x	x	✓	✓	✓	✓	✓	✓	x	✓	✓	x	x	✓	✓	Mar 2007: Cohorting of patients and staff; 'snow ball' active surveillance sampling[1]
	x	✓	x	✓	✓	✓	✓	✓	✓	x	✓	✓	x	x	✓	✓	Aug 2008: Weekly active surveillance of ICU
	x	✓	x	✓	✓	✓	✓	✓	✓	x	✓	✓	x	x	✓	✓	Mar 2009: Active surveillance of patients on admission to ER
Poulou 2012 [99] (Staged three-phase intervention)	x	x	x	x	x	x	x	x	x	x	✓	✓	x	x	✓	✓	Phase 1 (2009–)
	x	x	x	x	x	✓	✓	x	x	x	✓	✓	x	x	✓	✓	Phase 2 (Jan 2010–)
	x	x	x	x	x	✓	✓	✓	✓	x	✓	✓	x	x	✓	✓	Phase 3 (2011–)

Study reference (first author, year)	Active screening on admission to hospital	Active screening on admission to specific ward/unit	Pre-emptive isolation of patients on admission	Contact tracing	Active surveillance during the outbreak	Patient cohorting	Patient isolation	Nursing (or staff) cohorting	Dedicated nursing or other types of dedicated care by staff members	Bathing in anti-septic	Contact pre-cautions	Hand hygiene	Ward closure	Hospital closure	Patient record flagging	Other[2]	Further details
Schwaber 2014 [50,100] and 2014 [100]	x	x	X	x	X	✓	✓	✓	✓	x	✓	✓	x	x	✓	✓	

✓ Component is included; X component is not included

[1] *'Snow ball' active surveillance: screening of patients in the same room as newly identified carriers of CRKP*

[2] *Infection control measures periodically mentioned, not standardly implemented in bundles of infection control measures; supported by very limited evidence. Examples: visitor education (95), assigned patient transport (95), and dedicated shared equipment (96). Described as 'other' since further research is required.*

6.2.2 Methodological quality of the studies (Downs & Black's quality assessment criteria)

The overall quality of the six studies included in the analysis was at best moderate (see Table 3). None of the studies was a controlled intervention. However, all studies adequately described their stated interventions (Downs & Black, criterion 4) and study findings (Downs & Black, criterion 6). All were carried out in representative populations (Downs & Black, criterion 12) and settings (Downs & Black, criterion 13). The majority of studies, apart from Poulou 2012 [99], also clearly described the study aims and outcomes (Downs & Black, criteria 1 and 2). Elements of bias were present in all studies not only inherently due to the observational study design, but also because certain criteria in the Downs & Black checklist (see Table 3) were not met. The presence of bias affects the validity and reliability of the findings.

One particularly poorly reported area in the majority of the publications was patient characteristics (Downs & Black, criterion 3), with only one study reporting this criterion adequately (Chitnis 2012 [96]) and another only partially (Borer 2011 [101]). This makes comparisons difficult as it is not possible to objectively assess whether the studied populations were comparable in terms of demographics. None of the studies reported adverse events as a result of their interventions (Downs & Black, criterion 8). Compliance was poorly reported (Downs & Black, criterion 19), with only two studies reporting full compliance results for interventions (Ciobotaro 2011 [97], Schwaber 2014 [50,100]) and three studies reporting compliance results for some stages of phased measures. Compliance rates were generally low to moderate (Chitnis 2012 [96], Cohen 2011 [98], Poulou 2012 [99]).

Before-and-after studies are subject to bias and the risk of confounding by selecting patients from different time periods (pre-intervention and post-intervention) (Downs & Black, criterion 22). Additional factors may have an influence on the spread of CPE/CRE. This was acknowledged by some of the authors, who also conceded that assessing the influence of these factors was difficult. None of the studies accounted for potential confounding when analysing findings (Downs & Black, criterion 25). Ideally, a controlled study design with a single infection control measure is used to make a proper assessment of effectiveness. This, however, is often difficult as studies are often carried out under outbreak conditions or where swift action (not necessarily under experimental controls) is required in order to prevent the serious consequences of CPE/CRE infection and transmission. It may be possible to conduct good controlled studies in areas where CPE/CRE are endemic, provided there is sufficient funding and time. In addition, no information on loss of patients to follow-up (Downs & Black, criterion 26) was given in any of the publications, but this may again be due to the nature of reporting in acute healthcare settings, where emergency infection control procedures are put into place.

No other apparent risk of bias was evident or was reported for Poulou 2012 [99]. The remaining publications did not specifically report on risk of bias; however, some problems which may influence the risk of bias in these studies were reported by the authors or were evident from the findings.

Four of the studies appeared to be ambidirectional in that they prospectively followed the effects of the intervention, but retrospectively identified pre-intervention infection levels (Borer 2011 [101], Chitnis 2012 [96], Ciobotaro 2011 [97], Schwaber 2014 [50,100]). The reliance on retrospective data suggests that the data may not be reliable or suboptimal. More specifically, Chitnis 2012 [96] may have underestimated the clinical impact of CRE among patients as it was not possible to retrospectively determine whether sputum or urine cultures positive for CRE represented true infections. .Schwaber 2014 [50,100] also refers to the possibility that case numbers were overestimated in the pre-intervention period. In addition, detection methods for CRE improved during the study period, which may have led to allocation bias and the underestimation of the magnitude of the intervention.

The staged infection control measures used in Cohen 2011 [98] made it difficult to determine the independent effect of each infection control measure, and compliance with the various measures was not always adequate. In Schwaber 2014 [50,100], compliance data could not be objectively verified due to the way compliance data were collected and the hospital staff's insufficient reports on adherence to infection control measures. The authors also stated that enhanced awareness of, and feedback on, infection control activities may have also affected the study results ('the Hawthorne effect'). This factor is likely to be shared by the other before-and-after studies included in this review.

Table 3: Summary of individual study quality using Downs & Black criteria

Study name	Downs & Black assessment criterion no.																								
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Borer 2011 [101]					■		■	■						X	X	X	X				X	■	X	X			
Chitnis 2012 [96]					■		■	■						X	X	X	X				X	■	X	X			
Ciobotaro 2011 [97]			■		■			■		■				X	X	X	X				X	■	X	X			
Cohen 2011 [98]			■		■			■						X	X	X	X				X	■	X	X			
Poulou 2012 [99]		■	■		■			■						X	X	X	X				X	■	X	X			
Schwaber 2014 [50,100]			■		■			■						X	X	X	X				X	■	X	X			

Blank = yes, criterion met; black = no, criterion not met; grey = unclear/NA if criterion met; X = not applicable

1 Is the hypothesis/aim/objective of the study clearly described?
2 Are the main outcomes to be measured clearly described in the introduction or methods section?
3 Are the characteristics of the patients included in the study clearly described?
4 Are the interventions of interest clearly described?
5 Are the distributions of principal confounders in each group of subjects to be compared clearly described?
6 Are the main findings of the study clearly described?
7 Does the study provide estimates of the random variability in the data for the main outcomes?
8 Have all important adverse events that may be a consequence of the intervention been reported?
9 Have the characteristics of patients lost to follow-up been described?
10 Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value <0.001?
11 Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
12 Were the subjects who were prepared to participate representative of the entire population from which they were extracted?
13 Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?
14 Was an attempt made to blind study subjects to the intervention they have received?
15 Was an attempt made to blind those measuring the main outcomes of the intervention?
16 If any of the results of the study were based on 'data dredging', was this made clear?
17 In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?
18 Were the statistical tests used to assess the main outcomes appropriate?
19 Was compliance with the intervention/s reliable?

20 Were the main outcomes used accurate (valid and reliable)?

21 Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?

22 Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?

23 Were study subjects randomised to intervention groups?

24 Was the randomised intervention assignment concealed from both patients and healthcare staff until recruitment was complete and irrevocable?

25 Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?

26 Were losses of patients to follow-up taken into account?

27 Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?

6.3 Single-faceted measures

None of the studies reported data for single infection control measures.

6.4 Multi-faceted intervention bundles

All the studies included in the analysis assessed the effects of introducing a bundle of infection control measures. Details of the measures are given in Table 4, compliance assessments can be found in in Table 5, and the study results are in Table 6.

Four studies reported infection control measures implemented during an outbreak with CRE: three studies were on outbreaks due to CRKP identified in acute care hospitals in Israel between 2006 and 2007 (Borer 2011 [101], Ciobotaro 2011 [97], Cohen 2011 [98]), one study was due to a CRE outbreak (*K. pneumoniae*, *E. coli* and *Enterobacter aerogenes*), which began in February 2010 in a US LTCF (Chitnis 2012 [96]). Three of the four studies attempted to measure compliance. Chitnis 2012 [96] found low compliance with hand hygiene (31% of opportunities), inadequate cleaning of shared portable medical equipment and surfaces, and suboptimal maintenance of invasive devices. However, better compliance was seen for contact precautions (gloves worn on 77% and gowns worn in 89% of opportunities). Ciobotaro 2011 [97] found that compliance with active surveillance increased from 20% to 89% during the study. Cohen 2011 [98] also measured compliance with active surveillance and found that the mean rate of compliance with the active surveillance protocol was 43% (SD 10%).

All three studies from Israel reported statistically significant reductions in the prevalence or incidence of CRKP with some of the measures. Ciobotaro 2011 [97] measured the incidence of new clinical cases (identified from blood culture or from a sample of pleural or peritoneal fluid, urine, respiratory tract, catheter tip, wound culture, or wound drain) of CRKP (including KPC-3) reported to the infection control unit, which decreased from 3.4 to 0.5/10 000 patient days over 18 months ($p<0.001$). Borer 2011 [101] measured both CRKP prevalence and incidence. Prevalence was defined as the number of patients with positive rectal screening culture on admission, and incidence as the number of newly identified positive clinical cultures (assumed to indicate infections) per month. Both prevalence and incidence were significantly reduced over a four-year period: prevalence dropped from 10.4 to 2.3/100 patients ($p<0.001$); incidence from 5.26 to 0.18/10 000 patient days ($p<0.001$).

Cohen 2011 [98] assessed cumulative measures implemented in four stages during the outbreak: (1) single room isolation and contact precautions; (2) plus patient and nurse cohorting, screening of patients in the same room as newly identified carriers, defined as 'snow ball active surveillance sampling', and continued cohorting of returning patients; (3) plus weekly active surveillance in the ICU; (4) plus active surveillance on admission to the emergency department. Faecal, rectal, or perianal surveillance cultures were obtained. The study found that the prevalence of CRKP (clinical and surveillance cultures) increased during the first phase, but stabilised and began to fall from phase two onwards (from 10.4 to 20.2, then to 13.5/1 000 beds between March 2006 and August 2010). For CRKP incidence (clinical and surveillance cultures), the phase one components were again unsuccessful, and the results followed a similar pattern to prevalence (increased from 8.4 to 13.4 then dropped to 4.3/1 000 beds). For both outcomes there were no statistically significant differences between phases two and three, or between phases three and four. Although both incidence and prevalence continued to fall after active surveillance was introduced, only the phase two components (patient and nurse cohorting, 'snow ball' active surveillance sampling (defined as patient and nurse cohorting, screening of patients in the same room with newly identified carriers) and continued cohorting of returning patients) were associated with significant declines in both outcomes. The study concluded that 'cohorting patients [was] the most successful intervention, and its effect overshadowed those of the other infection control interventions that were implemented'.

A US study reported a CRE outbreak in an LTCF (Chitnis 2012 [96]). The bacterial species reported were *K. pneumoniae*, *E. coli*, and other *Enterobacter* spp. The study assessed cumulative measures implemented in

three phases: (1) contact precautions and rectal screening cultures on admission; (2) plus active surveillance (on admission and via point prevalence surveys), hand hygiene, patient and nurse cohorting; (3) plus daily audits, assessments of hand hygiene and invasive device use, and dedicated nurses and equipment [96]. These measures were associated with significant decreases (p-values NR) in CRE prevalence and the number of newly detected cases between July 2010 (49% overall; 44% newly detected) and July 2011 (8% overall; 0% newly detected). There was also a statistically significant decrease in incidence (p=0.01) during the intervention period (July 2010 to July 2011). However, results were only reported overall, and not before and after each phase of the implementation, so it was not possible to assess the impact of each additional group of measures. Sixteen present-on-admission CRE cases were detected between 1 March 2009 and 28 February 2011; these cases were transferred to the studied LTCF from several different acute care hospitals in the surrounding region, with one acute care hospital accounting for 44% (n=7) of cases. During this period, this acute care hospital accounted for the second highest number of admissions to this LTCF. CRKP was recovered from 15 (94%) of 16 present-on-admission cases; carbapenem-resistant *E. coli* was detected in one patient.

Two studies were performed during CPE outbreaks, both in endemic areas (Schwaber 2014 [50,100] in Israel, Poulou 2012 [99] in Greece). Schwaber 2014 [50,100] measured compliance with isolation guidelines (only one of a number of infection control measures implemented), finding that there was almost universal compliance during the study period. The study reported a direct correlation between compliance and successfully containing transmission (p=0.02). This was the only study to report combined results, rather than for a single centre, giving monthly incidence rates for CRE (*Klebsiella* spp., *Enterobacter* spp., *E. coli*, *Proteus* spp. and *Providencia* spp.) from 27 hospitals (but without any indication of variation between hospitals). The measures halted the steep increase in incidence, and there was a steady downward trend (185 new cases, 55.5/100 000 patient days pre-intervention March 2007 to 45 new cases, 11.7/100 000 patient days May 2008). In a follow-up publication [100] in 2014, the authors reported a continued decrease in incidence to 4.8/100 000 patient days in 2012. In addition, point prevalence surveys of CRE carriage demonstrated that the carriage prevalence among patients not previously known to be carriers dropped from 12.1% in 2008 to 7.9% in 2011 (p=0.008).

The second study (Poulou 2012 [99]) also assessed phased infection control measures to decrease the incidence of KPC-2 and VIM-1 producing *K. pneumoniae*. The interventions included: contact precautions (gloves and gowns), patient flagging, some patient cohorting, and a medical record review of positive cases diagnosed in 2009. Additional measures included the immediate notification of the staff when new cases were detected, patient cohorting or isolation, more stringent hand hygiene, environmental cleaning, informing relatives/carers of infection control measures, and compliance assessment based on feedback from 2010. A third tier of measures included more single ICU rooms, dedicated nursing, further improvements in hand hygiene, active surveillance (rectal cultures) within 24 hours, and the promotion of infection control and checks by an infection control nurse in 2011. Compliance with hand hygiene increased from 22% to 43% in hospital wards and from 27% to 56% in the ICU. The incidence of carbapenemase-producing *K. pneumoniae* cases decreased between 2009 and 2010, but this decrease was not statistically significant (p=0.075 all cases, p=0.058 hospital-acquired cases). By 2011, after additional measures had been implemented, there was a statistically significant decrease in new cases (from 0.52/1 000 patient days in 2009 to 0.21/1 000 patient days in 2011, p=0.0028). Out of 73 cases, 28 were community-onset cases and 45 were hospital-acquired. The 28 community-onset cases were attributed to *K. pneumoniae* isolates producing either KPC-2 carbapenemase (n=23) or both KPC-2 and VIM-1 carbapenemases (n=5). Medical histories revealed that patients with community-onset infections had been hospitalised over the preceding three months in various tertiary-care hospitals in Greece and all cases were therefore categorised as 'healthcare-associated: imported from another institution'. Based on molecular typing, carbapenemase gene content, and the proximity of the patients, 23 of the 45 hospital-acquired cases were epidemiologically linked to imported cases and thus considered importation-associated. In total, 53 KPC-2, 9 KPC-2 VIM-1, and 12 VIM-1 phenotypes were identified (community- and hospital-acquired).

Table 4: Measures to control the spread of CPE infection in multi-faceted studies

Measure	No. of studies	Study IDs
Active screening on admission to hospital	3	Borer 2011 [101]; Chitnis 2012 [96]; Ciobotaro 2011 [97]
Active screening on admission to specific ward/unit	4	Borer 2011 [101]; Chitnis 2012 [96]; Ciobotaro 2011 [97]; Cohen 2011 [98]
Pre-emptive isolation of patients on admission	1	Borer 2011 [101]
Contact tracing	2	Borer 2011 [101]; Cohen 2011 [98]
Active surveillance during the outbreak	4	Borer 2011 [101]; Chitnis 2012 [96]; Ciobotaro 2011 [97]; Cohen 2011 [98]
Patient cohorting	6	Borer 2011 [101]; Chitnis 2012 [96]; Ciobotaro 2011 [97]; Cohen 2011 [98]; Poulou 2012 [99] Schwaber 2014 [50,100]

Measure	No. of studies	Study IDs
Patient isolation	6	Borer 2011 [101]; Ciobotaro 2011 [97]; Cohen 2011 [98]; Poulou 2012 [99]; Schwaber 2014 [50,100]
Nursing (or staff) cohorting	4	Chitnis 2012 [96]; Cohen 2011 [98]; Poulou 2012 [99]; Schwaber 2014 [50,100]
Dedicated nursing or other types of dedicated care by staff members	6	Borer 2011 [101]; Chitnis 2012 [96]; Ciobotaro 2011 [97]; Cohen 2011 [98]; Poulou 2012 [99]; Schwaber 2014 [50,100]
Bathing in antiseptic	0	-
Contact precautions	6	Borer 2011 [101]; Chitnis 2012 [96]; Ciobotaro 2011 [97]; Cohen 2011 [98]; Poulou 2012 [99]; Schwaber 2014 [50,100]
Hand hygiene	6	Borer 2011 [101]; Chitnis 2012 [96] Ciobotaro 2011 [97]; Cohen 2011 [98]; Poulou 2012 [99]; Schwaber 2014 [50,100]
Ward closure	0	-
Hospital closure	0	-
Patient record flagging	5	Borer 2011 [101]; Ciobotaro 2011 [97]; Cohen 2011 [98]; Poulou 2012 [99]; Schwaber 2014 [50,100]
Other	6	Borer 2011 [101]; Chitnis 2012 [96]; Ciobotaro 2011 [97]; Cohen 2011 [98]; Poulou 2012 [99]; Schwaber 2014 [50,100]

Table 5: Summary of compliance assessment in multi-faceted studies to control the spread of CPE

Study ID	Compliance tested	Details (assessed measure and results of compliance assessment)
Borer 2011 [101]	Yes	The fourth component (out of five) included 'enforcement and compliance with hand hygiene, contact precautions and disinfection protocols'. However, there were no numeric results reported for compliance, apart from that the disinfection protocol was 'rigorously applied'; hand hygiene compliance was not measured when samples were obtained.
Chitnis 2012 [96]	Phase 1 and 2: No Phase 3 and 4: Yes	Hand hygiene. During March 2011 (Phase 3 and 4 only), hand hygiene was successfully performed at 31% (30/96) of opportunities. Contact precautions. Gloves worn during 77% (78/102) of opportunities; gowns in 89% (78/88) of opportunities. Suboptimal maintenance practices for invasive devices were noted, including inconsistent performance of hand hygiene prior to accessing central venous catheters. Cleaning. Healthcare workers did not adequately clean and disinfect some shared portable medical equipment (e.g. X-ray and ultrasound machines); high-touch surfaces (e.g. medication cabinets in patient rooms) were also not cleaned and disinfected during observations.
Ciobotaro 2011 [97]	Yes	Active surveillance. The rate of implementation of active surveillance increased from 20% (84/413) in August 2008 to 89% (503/562) in June 2010. The performance rate also exceeded 100% during the first months of 2010.
Cohen 2011 [98]	Phase 1: No/NR Phase 2: Yes Phase 3: Yes Phase 4: Yes	Emergency department screening and isolation/cohorting. Mean monthly % (SD) of patient days during which CRKP carriers were appropriately cohorted was 71% (SD 20%) in Phase 2. Active surveillance (Phase 3 and 4) identified 42% (104/251) of positive cases by ICU screening and 61/251 (24%) by active screening in ER; remaining 86/251 (34%) identified by active surveillance of contacts of newly identified. Mean rate of compliance in ER with the active surveillance protocol was 43% (SD 10%).
Poulou 2012 [99]	Phase 1: No Phase 2: Yes Phase 3: Yes	Hand hygiene. During 2010 and 2011 (phase 2 and 3), hand hygiene compliance improved from 22% to 43% in hospital wards and from 27% to 56% in the ICU. Patient isolation. Isolation in single room was possible in 36.4% (8/22) of cases during 2010 and in 73.3% (11/15) of cases during 2011. Improved from 22% to 43% in hospital wards and 27% to 56% in the ICU.
Schwaber 2014 [50,100]	Yes	Isolation guidelines. Almost universal compliance with guidelines during the entire intervention period (i.e. labelling for contact precautions, use of gowns and gloves, physical separation). Compliance with dedicated nursing staffing was not uniform throughout, with upward trend during study period. There was a direct correlation between compliance with isolation guidelines and success in containment of transmission (p=0.02); compliance neutralised the effect of carrier prevalence on new incidence (p=0.03).

ER = emergency room; HCW = healthcare worker; p = p-value; ICU = intensive care unit; L = litre; pt = patient; SD = standard deviation; CRKP = carbapenem-resistant K. pneumoniae

Table 6: Summary of findings from infection control measures in multi-faceted studies to control the spread of CPE

Study, location, type	Infection control measures	Compliance assessed	Bacteria (outbreak-based or not)	Outcome measure	Baseline data (time period)	Follow-up data (time period)	Analysis results
Borer 2011 [101] Israel Before-and-after study	A (rectal), B (rectal), C, D, E (rectal), F, G, I, K, L, O, P (carbapenem-restriction, environmental cleaning and hand and environmental cultures, at epidemiologists discretion; staff education)	Yes (disinfection protocol was rigorously applied but hand hygiene compliance was not measured when samples were obtained)	Carbapenem-resistant *Klebsiella pneumoniae (CRKP)* (outbreak)	*Prevalence*: number of patients with positive rectal screening culture on admission (isolates from first rectal culture) *Incidence:* number of newly identified patients with positive result from clinical culture (considered to indicate infection) (CRKP-IN) per month (infection density)	*Prevalence* 10.4/100 patients (May–Dec 2007) *Incidence* 5.26/10 000 patient days (CRKP-IN) (May 2006–Apr 2007 pre–intervention)	*Prevalence* 2.31/100 patients (May–Dec 2010) *Incidence* 0.18/10 000 patient days (CRKP-IN) (Jan–May 2010)	Total prevalence for admitted patients was significantly reduced over a four-year period 10.4 in 2007, 6.09 in 2008, 3.65 in 2009, 2.31 in 2010 (χ^2 test for trend P<0.001). Infection density was also significantly reduced (P<0.001) and nosocomial *K. pneumoniae* infections were diagnosed.
Chitnis 2012 [96] USA Before-and-after study	A (urine/sputum later rectal), B (urine/sputum later rectal), E (urine/sputum later rectal), F, H, I, K, L, P (environmental cleaning reminders and staff education) Cumulative phase intervention from July 2010 to July 2011. 1: Contact precautions, samples on admission. 2: Plus active surveillance of all patients, hand hygiene, patient and nurse cohorting 3: Daily audits and assessment of hand hygiene and invasive device use, dedicated nurses and equipment	Yes: at least 40 hours observation of healthcare staff, audits of hand hygiene, gown and glove use, use of invasive devices. In phase 3 (Mar 2011) hand hygiene was performed at 31% of opportunities, gloves worn at 77% and gowns worn at 89% of opportunities.	CRE including carbapenem-resistant *K. pneumoniae*, carbapenem-resistant *Enterobacter aerogenes*, and other *Enterobacter* spp. (outbreak)	*Prevalence*: monthly CRE prevalence on admission from screening (urine or sputum from Jan 2010 and rectal from July 2010) or clinical cultures (cases isolated within three days of admission/total monthly admissions). Overall prevalence (newly detected and known cases/total number at survey date) *Incidence:* number of CRE transmission cases (probable or possible)/total numbers of patient days	*Monthly prevalence* Median 0% (range 0–3% (Mar–Dec 2009) *Overall prevalence* 49% (44% newly detected) (27 July 2010) *Incidence* 3.6/1 000 patient days (Oct 2010)	*Monthly prevalence* Median 0% (range 0–5%) (Jan–June 2010) Median 3% (range 0–13%) (Jul 2010–Feb 2011) *Overall prevalence* 8% (0% newly detected) (26 July 2011) *Incidence* 0/1 000 patient days (June 2011)	There was a significant decrease in CRE prevalence and in the percentage of screened patients with newly detected CRE from July 2010– July 2011. No statistically significant trend in incidence was detected during March 2009–July 2011. However, when limiting the analysis to July 2010–July 2011, the period when interventions were implemented, there was a statistically significant decrease (P=0 .01) in incidence.
Ciobotaro 2011 [97] Israel Before-and-after study	A (rectal), B (rectal), E (rectal), F, G, I, K, L, O, P (environmental cleaning policy and staff education)	Yes: active surveillance by measuring proportion of patients actually screened. This increased from 20% to 89%.	CRKP (also include KPC-3) (outbreak)	*Incidence:* new clinical cases (blood culture/pleural/ peritoneal fluid/urine/ respiratory tract/ catheter tip/wound culture/wound drain) reported to the infection control unit	*Incidence* 3.4/10 000 patient days (May–Dec 2006, no cases Jan–May 2006)	*Incidence* 0.5/10 000 patient days (Jan 2008–June 2010)	Poisson segmented regression demonstrated a significant difference in slope before and after the intervention (p<0.001). The negative slope indicated that during each month post-intervention the number of CRKP cases decreased.

Study, location, type	Infection control measures	Compliance assessed	Bacteria (outbreak-based or not)	Outcome measure	Baseline data (time period)	Follow-up data (time period)	Analysis results
Cohen 2011 [98] Israel Before-and-after study	B (rectal), D, E (rectal, faecal, perinatal), F, G, H, I, K, L, O, P (environmental cleaning) Cumulative phase intervention starting in Mar 2006 at start of epidemic. 1: Single-room isolation and contact precautions 2: Cohorting of patients and nursing staff, screening of patients in the same room as newly identified carriers ('snow ball' active surveillance), and continued cohorting of returning patients 3: Weekly active surveillance in the ICU 4: Active surveillance on admission to the emergency dept.	Yes: for patient cohorting and emergency department screening. Mean patient days with carrier cohorting was 71%. Mean rate of emergency department compliance with active surveillance was 43%.	CRKP (outbreak)	*Prevalence*: mean number of cases per month calculated from weekly point-prevalence surveys (both clinical and faecal, rectal, or perianal surveillance cultures) *Incidence*: mean incidence of colonisation or infection (total number of cases acquired in hospital detected by clinical cultures)	*Prevalence* NR *Incidence* NR	*Prevalence* 10.4/1 000 beds (Mar 2006–Mar 2007) 20.2/1 000 beds (Apr 2007–Aug 2008) 17.4/1 000 beds (Sept 2008–Mar 2009) 13.5/1 000 beds (Apr 2009–Aug 2010) *Incidence* 8.4/1 000 beds (Mar 2006–Mar 2007) 13.4/1 000 beds (Apr 2007–Aug 2008) 8.3/1 000 beds (Sept 2008–Mar 2009) 4.3/1 000 beds (Apr 2009–Aug 2010)	*Prevalence* Prevalence rates increased as epidemic control failed during intervention 1 (linear regression model slope 2.0). There was a significant change in slope (-0.01, p<0.001) for intervention 2 compared to 1, but no significant changes for intervention 3 compared with 2 or 4 compared with 3. Prevalence rates stabilised and began to fall from intervention 2 onwards. *Incidence* Intervention 1 was not successful; the incidence increased in March 2007 (linear regression model slope (1.9)). There was a significant change in slope (-0.7, p<0.007) for intervention 2 compared with 1, but no significant changes for intervention 3 compared with 2, or 4 compared with 3. Only intervention 2 was associated with significant declines in both prevalence and incidence rates.
Poulou 2012 [99] Greece Before-and-after study	F, G, H, I, K, L, P (environmental cleaning after discharge of positive patients) Phased intervention: 2009 (use of gloves and gowns, hand hygiene, some patient cohorting) 2010 (reinforced measures) 2011 (additional measures including isolation, dedicated nursing, strengthened hand hygiene)	Yes: hand hygiene Hand hygiene improved from 22% to 43% in hospital wards and 27% to 56% in the ICU.	*K. pneumoniae* producing either KPC-2 or VIM-1 or, producing both KPC-2 and VIM-1) (no outbreak)	*Incidence*: incidence of imported, hospital-acquired and overall cases (community imported or hospital acquired) *Cases*: number of cases identified through clinical isolates	*Incidence 2009* Overall 0.52/1 000 patient days Imported 0.16/1 000 patient days Hospital-acquired 0.36/1 000 patient days *Cases 2009* 23 (63.9%) KPC-2 5 (13.9%) KPC-2, VIM-1 8 (22.2%) VIM-1	*Incidence 2010* Overall 0.32/1 000 patient days Imported 0.13/1 000 patient days Hospital-acquired 0.19/1 000 patient days *Incidence 2011* Overall 0.21/1 000 patient days Imported 0.11/1 000 patient days Hospital-acquired 0.1/1 000 patient days *Cases 2010* 16 (72.7%) KPC-2 4 (18.2%) KPC-2, VIM-1 2 (9.1%) VIM-1 *Cases 2011* 13 (86.7%) KPC-2 0 (0%) KPC-2, VIM-1 2 (13.3%) VIM-1	Compared with 2009, there was a decline in the 2010 rate of cases (p= 0.075). Hospital-acquired cases declined between 2009 (0.36/1 000 patient days) and 2010 (0.19/1 000 patient days; p=0.058). In 2011, the rate of new cases declined significantly from 2009 (p=0.0028). The incidence of new cases in the entire post-intervention period (Jan 2010–Dec 2011) was significantly lower than the preintervention period (p=0.0051). 28/73 were community acquired* and 45/73 were considered hospital-acquired cases.

Study, location, type	Infection control measures	Compliance assessed	Bacteria (outbreak-based or not)	Outcome measure	Baseline data (time period)	Follow-up data (time period)	Analysis results
Schwaber 2014 [50] [100] Israel Before-and-after study	F, G, H, I, K, P	Yes: compliance with isolation guidelines.	CRE including *Klebsiella* spp., *Enterobacter* spp., *E. coli*, *Proteus* spp. and *Providencia* spp. (no outbreak)	*Incidence*: monthly incidence of cases over time (combined over 27 hospitals) *Cases*: identified from clinical cultures **Updated results from 2014 paper** *Prevalence:* Prevalence of carriage in patients who were previously not known to be carriers of CRE	*Incidence* 55.5/100 000 patient days 185 cases (new cases pre-intervention Mar 2007) **Updated results from 2014 paper** 12.1% in 2008	*Incidence* 11.7/100 000 patient days 45 cases (new cases May 2008) **Updated results from 2014 paper** 8.2/100 000 patient days (2009) 6.8/100 000 patient days (2010) 5.8/100 000 patient days (2011) 4.8/100 000 patient days (2012) **Updated results from 2014 paper** 7.9% in 2011 (P = .008)	The intervention halted the steep increase in incidence. From May 2007 onwards there was a steady downwards trend. The final value was 21% of the Mar 2007 peak (p<0.001). Incidence continued to decline up to 2012. Significant decrease in prevalence of CRE carriage in patients no previously known as carriers (2008 to 2011); P=0.008.

A: active screening on hospital admission, B: active screening on ward/unit admission, C: pre-emptive isolation on admission, D: contact tracing, E: active surveillance during the outbreak, F: patient cohorting, G: patient isolation, H: nursing/staff cohorting, I: dedicated nursing or other types of dedicated care by staff members, J: bathing with antiseptic, K: contact precautions, L: hand hygiene, M: ward closure, N: hospital closure, O: patient record flagging, P: other (e.g. restrictions in antibiotic use).

** Community-onset cases were attributed to* K. pneumoniae *isolates producing either the KPC-2 carbapenemase (n=23) or both the KPC-2 and VIM-1 carbapenemases (n=5). Medical histories revealed that patients with community onset infections had been hospitalised over the preceding three months in various tertiary-care hospitals in Greece. Therefore, all of these cases were considered 'healthcare-associated: imported from another institution'. Based on molecular typing, carbapenemase gene content, and the proximity of the patients, 23 of the 45 hospital-acquired cases were epidemiologically linked to imported cases and were considered importation-associated.*

6.5 Summary of evidence to support individual infection control measures

The following section summarises the evidence on the effectiveness of the most frequently reported infection control measures as described in the six included studies. Limitations include the low quality of some of the included studies, the lack of control groups, and the fact that all studies evaluated multi-faceted infection control measures and did not examine each intervention in isolation. Therefore, these summaries should be interpreted with caution. Further research is needed before definitive statements can be made.

6.5.1 Active screening and surveillance

The original 2011 ECDC review [1] found seven studies which assessed active surveillance cultures as part of a bundle of infection control measures and found this intervention to be effective.

In this updated 2013 review, four studies included active screening on admission to a specific ward/unit and surveillance during an outbreak, as part of an infection control bundle (Borer 2011 [101]; Chitnis 2012 [96]; Ciobotaro 2011 [97], Cohen 2011 [98]). All but Cohen 2011 [98] also screened patients on admission to the hospital. Only two of the studies (Ciobotaro 2011 [97] and Cohen 2011 [98]) assessed compliance with screening/surveillance, and one found compliance to be suboptimal (Cohen 2011 [98]). No study assessed screening/surveillance as a single intervention. Screening involved rectal cultures (Borer 2011 [101]; Ciobotaro 2011 [97], Cohen 2011 [98]) or a combination of either faecal, rectal, or perianal cultures (Chitnis 2012 [96]). Two studies found significant reductions in CRKP following outbreaks in acute care hospitals in Israel (Borer 2011 [101]; Ciobotaro 2011 [97]). One further outbreak study from a US LTCF (Chitnis 2012 [96]) also found significant decreases in CRE (carbapenemase-producing *Klebsiella pneumoniae*, *Enterobacter aerogenes* and other *Enterobacter* spp.) prevalence and the number of newly detected cases (including cases transferred from several other acute care hospitals in the surrounding region). One further study (Cohen 2011 [98]) from Israel found significant reductions in both CRKP incidence and prevalence, but reported that the addition of active surveillance (either in the ICU or on admission to the emergency department) did not have additional significant effects as 'cohorting patients [was] the most successful intervention, and its effect overshadowed those of the other infection control interventions that were implemented'.

In summary, there is evidence to suggest that active rectal screening/surveillance on admission to hospital or a specific ward and during an outbreak can effectively limit and prevent the spread of CRKP and/or carbapenemase-producing *K. pneumoniae* (evidence level ++).

6.5.2 Patient cohorting

The original 2011 ECDC review [1] found one study [83] which assessed the effects of patient cohorting and found it effective in controlling the spread of CPE as part of a multi-faceted infection control bundle.

In this updated 2013 review, all six included studies incorporated patient cohorting as part of an infection control bundle. However, only two studies assessed compliance with patient cohorting (Cohen 2011 [98], Schwaber 2014 [50,100]), and none of the studies assessed patient cohorting as a single intervention. All studies reported decreases in CPE/CRE. Three studies reported significant reductions in CRKP during outbreaks in acute care hospitals in Israel (Borer 2011 [101], Ciobotaro 2011 [97], and Cohen 2011 [98]); and one US outbreak study (Chitnis 2012 [96]) in an LTCF reported significant reductions in CRE prevalence (carbapenemase-producing *K. pneumoniae*, *Enterobacter aerogenes* and other *Enterobacter* spp.). The US study also reported a decrease in the number of newly detected cases, including cases transferred from surrounding hospitals. Cohen 2011 [98] concluded that patient cohorting was the single most successful intervention. Two other studies, which were not carried out as part of an outbreak investigation, also reported reductions in CPE: a study in a Greek acute care hospital (Poulou 2012 [99]) which included patients with healthcare-associated infections imported from another institution reported non-significant decreases in the incidence of KPC-2 and VIM-1 producing *K. pneumoniae*. A study conducted in an acute care hospital in Israel (Schwaber 2014 [50,100]) reported significant decreases in CRE (*Klebsiella* spp., *Enterobacter* spp., *E. coli*, *Proteus* spp. and *Providencia* spp.). CRE carriage among patients not previously known to carry CRE was also reported to have decreased (Schwaber 2014 [100]).

In summary, there is evidence to suggest that patient cohorting during an outbreak is effective for limiting and preventing the spread of CRKP and/or carbapenemase-producing *K. pneumoniae* (evidence level ++).

6.5.3 Patient isolation

The original 2011 ECDC review [1] found two studies [81,87] on single-room isolation as part of an apparently effective infection control bundle.

This updated 2013 review identified four studies evaluating patient isolation as part as an infection control bundle (Borer 2011 [101], Cohen 2011 [98], Poulou 2012 [99], Schwaber 2014 [50,100]). Three of the studies assessed compliance with patient isolation (Cohen 2011 [98], Poulou 2012 [99], Schwaber 2014 [50,100]), but none of the studies assessed patient isolation as a single intervention. One study, conducted during a CRKP outbreak in an Israeli acute care hospital, found significant reductions in CPE (Borer 2011 [101]). The studies by Poulou 2012 [99] and Schwaber 2014 [50,100], which did not focus on outbreaks, reported reductions in CPE which were not described as significant. Both studies focussed on evaluating cases of KPC-2 and VIM-1 producing *K. pneumoniae*. Poulou 2012 [99] included cases transferred from surrounding hospitals, and Schwaber 2014 [50,100] reported CRE levels (*Klebsiella* spp., *Enterobacter* spp., *E. coli*, *Proteus* spp. and *Providencia* spp.). The 2014 study also reported a direct correlation between compliance with isolation guidelines and the successful containment of transmission, including a reduction in the carriage of CRE in patients not previously known to carry CRE. However, one other study carried out in an acute care hospital during an outbreak in Israel found that rates of CRKP increased despite single-room isolation and contact precautions (Cohen 2011 [98]).

In summary, there is evidence to suggest that patient isolation is effective for limiting and preventing the spread of CRKP and/or carbapenemase-producing *K. pneumoniae* (evidence level ++).

6.5.4 Nursing (or staff) cohorting

The original 2011 ECDC review [1] found five studies assessing cohorted nursing care as part of a bundle of infection control measures [82-85,91] and all five studies appeared to show that the multi-faceted intervention bundles were effective in reducing the spread of CPE.

This updated 2013 review identified four studies that evaluated nurse cohorting (Chitnis 2012; [96] Ciobotaro 2011 [97]; Cohen 2011 [98]; Schwaber 2014 [50,100]) as part of an infection control bundle. None of the studies addressed compliance with nursing (or staff) cohorting specifically, but one study (Cohen 2011 [98]) reported that general compliance with cohorting was 71%. No study assessed the specific effects of nursing (or staff) cohorting alone. All four studies reported reductions in CPE levels. Two outbreak studies, one in a US LTCF (Chitnis 2012 [96]) and one in an acute care hospital in Israel (Ciobotaro 2011 [97]) reported decreases in CRE, including carbapenemase-producing *K. pneumoniae*, *Enterobacter aerogenes* and other *Enterobacter* spp. (Chitnis 2012 [96]) and CRKP (Ciobotaro 2011 [97]). Schwaber 2014 [50,100]) found significant reductions in CRE including *Klebsiella* spp., *Enterobacter* spp., *E. coli*, *Proteus* spp. and *Providencia* spp. and a significant reduction in carriage among patients not previously known to carry CRE. Cohen 2011 [98]) found significant reductions in CRKP during nurse

cohorting in combination with patient cohorting and 'snow ball' active surveillance sampling (defined as 'screening of patients in the same room as newly identified carriers').

In summary, there is evidence to suggest that nursing or staff cohorting is effective for limiting and preventing the spread of CPE and/or carbapenemase-producing *K. pneumoniae* (evidence level ++).

6.5.5 Dedicated nursing or other types of dedicated care by staff members

The original 2011 ECDC review [1] found no specific evidence for dedicated nursing.

In this updated review, all six included studies featured dedicated nursing or other types of dedicated care by staff members as part of an infection control bundle. One study specifically assessed compliance with this intervention, but found that compliance with dedicated nursing was inconsistent, although there was an upward trend towards consistency during the study period (Schwaber 2014 [50]). None of the studies assessed the effects of dedicated nursing in isolation from other infection control measures

In summary, there is evidence to suggest that dedicated nursing or other types of dedicated care by staff members is effective for limiting and preventing the spread of CPE (evidence level ++).

6.5.6 Contact precautions

The original ECDC 2011 review [1] included four studies [81,82,85,86] examining the use of contact precautions as part of what appeared to be successful infection control bundles for CPE.

In this updated review, all six studies included contact precautions. Only one of the studies assessed compliance with this specific intervention (Chitnis 2012 [96]); glove use was 77% and gown use 89%, but suboptimal practices were noted for hand hygiene and invasive devices. None of the studies assessed the effects of contact precautions in isolation from the other components in the infection control bundles. Borer 2011 [101] and Ciobotaro 2011 [97] reported significant reductions in CPE levels during CKRP outbreaks, and Schwaber 2014 [50,100] reported lower CRE levels (including *Klebsiella* spp., *Enterobacter* spp., *E. coli*, *Proteus* spp. and *Providencia* spp.) under non-outbreak conditions. CRE carriage among patients not previously known to carry CRE was also reported (Schwaber 2014 [100]).

The remaining three studies introduced bundles of interventions in phases. One study (Chitnis 2012 [96]) reported significant decreases for overall CRE prevalence (including carbapenemase-producing *K. pneumoniae*, *Enterobacter aerogenes*, and other *Enterobacter* spp.) and a lower number of newly detected cases in an outbreak in a US LTCF. Poulou 2012 [99] associates declining numbers of new KPC-2 and VIM-1 producing *K. pneumoniae* infections with reinforced infection control measures, including gown and glove use. However, one study (Cohen 2011 [98]) reported that the first phase of measures (single-room isolation and contact precautions) failed as CRKP rates increased.

In summary, there is evidence to suggest that contact precautions is effective for limiting and preventing the spread of CPE (evidence level ++).

6.5.7 Hand hygiene

The original ECDC 2011 review [1] included one study [83] which examined the promotion of hand hygiene as part of an apparently successful CPE infection control bundle.

In this updated review, five studies also examined hand hygiene as part of a bundle of infection control measures (Borer 2011 [101], Chitnis 2012 [96], Ciobotaro 2011 [97], Cohen 2011 [98], Poulou 2012 [99]). Three of the studies assessed compliance with hand hygiene (Borer 2011 [101], Chitnis 2012 [96], Poulou 2012 [99]). No clear results were reported by Borer 2011 [101], and compliance appeared to low in the other two studies. None of the studies assessed the effects of hand hygiene in isolation from the other elements of the infection control bundles. Two of the studies, both from acute care hospitals in Israel, found significant reductions in CRKP (Borer 2011 [101]) and CRKP (including KPC-3-producing isolates) (Ciobotaro 2011 [97]). Three studies implemented infection control bundles in phases (Chitnis 2012 [96], Poulou 2012 [99], Cohen 2011 [98]). Chitnis 2012 [96] reported significant decreases for overall CRE prevalence (including carbapenemase-producing *K. pneumoniae*, *Enterobacter aerogenes* and other *Enterobacter spp*) and newly detected cases in an outbreak study in a US LTCF. Another study in a Greek acute care hospital, which was carried out in phases (Poulou 2012 [99]), reported a significant reduction in new cases of KPC-2 and VIM-1 producing *K. pneumoniae*, once reinforced infection control measures (e.g. hand hygiene) were implemented. Cohen 2011 [98] also found significant reductions in CRKP during an outbreak using a bundle of measures including enforced hand hygiene measures, but the effects in this study were dominated by the use of cohorting as part of the infection control bundle. Two of the studies reported the inclusion of imported cases from other hospitals (Chitnis 2012 [96], Poulou 2012 [99]). Only one study (Poulou 2012 [99]) provided practical guidance on hand hygiene, recommending the use of either antiseptic soap or alcohol-based hand rub

before and after contact with an infected patient. In addition, this study, along with Chitnis 2012 [96], included cases that were associated with the transfer of patients from other hospitals.

In summary, there is evidence to suggest that hand hygiene is effective in the control of the spread of CPE (evidence level ++).

6.5.8 ICU or ward closure

The original 2011 review [1] included one study [83] examining the effects of ICU closure as part of a multi-faceted infection control intervention and found the bundle of measures to be effective at controlling the spread of CPE.

This updated 2013 review found no studies of ward or unit closure.

In summary, there is evidence to suggest that ICU or ward closure is effective to control the spread of CPE, but no new evidence has been identified in this updated review (evidence level ++).

6.5.9 Pre-emptive isolation of patients on admission

The original 2011 review [1] included one study [85] which found that pre-emptive isolation with contact precautions of high-risk patients was effective at controlling the spread of CPE.

In this updated review only one study (Borer 2011 [101]) found significant reductions in the prevalence and incidence of CRKP. However, pre-emptive isolation was implemented in parallel with a number of other measures and so the specific effects of this intervention are unclear.

In summary, there is evidence to suggest that pre-emptive isolation of patients on admission is effective in the control and spread of CRKP (evidence level ++).

6.5.10 Contact tracing

The original 2011 review [1] found no evidence regarding the effectiveness of contact tracing.

In this updated review, two studies included contact tracing (Borer 2011 [101], Cohen 2011 [98]). Neither assessed compliance with this type of intervention, and both studies assessed the intervention as part of an infection control bundle. Both studies were carried out during outbreaks in acute care hospitals in Israel and reported significant reductions in CKRP, but contact tracing was implemented in parallel with a number of other measures. No studies assessed contact tracing as a single infection control measure.

In summary, there is evidence to suggest that contact tracing is effective at controlling the transmission of CKRP (evidence level ++).

6.5.11 Bathing with antiseptic agents

Patient decolonisation by bathing with antiseptic agents was included as part of a successful CPE infection control intervention in two studies [84,85] included in the original 2011 ECDC review [1].

No further studies of bathing with antiseptic agents were identified during this updated review (2013).

In summary, there is evidence to suggest that bathing in antiseptic is effective to control the spread of CPE, but no new evidence was identified in this updated 2013 review (evidence level ++).

6.5.12 Antibiotic formulary change

Two studies, one from the original ECDC 2011 review [1] by Herbert et al. [87] and another from this updated review (Borer 2011 [101]) included antibiotic restriction as part of an effective CPE infection control bundle. Neither of these two studies, however, assessed this measure alone.

In this updated 2013 review, the study by (Borer 2011 [101]) included antibiotic (carbapenem) restriction as part of an infection control bundle, and compliance with the antibiotic restriction policy was assessed. Both total antibiotic consumption and consumption of meropenem were measured during the study period, but only the difference in meropenem consumption levels was statistically significant. In this study, which was carried out during an outbreak in an acute care hospital in Israel, a significant reduction in CKRP was reported.

In summary, there is evidence to suggest that an antibiotic formulary change is effective at controlling the transmission of CKRP (evidence level ++).

6.5.13 Environmental cleaning

The original ECDC review included three studies [83-85] which reported that environmental surface decontamination – as part of a multi-faceted infection control bundle – appeared to be beneficial with respect to the control of CPE.

In this updated review, four additional studies (Borer 2011 [101], Ciobotaro 2011 [97], Cohen 2011 [98], Poulou 2012 [99]) included environmental surface and item cleaning/disinfection (including physician's equipment such as stethoscopes and pens [101] and the rooms of positive patients after discharge [99]), as part of an infection control bundle. One study included the issuing of notes as a reminder to clean/disinfect surfaces and equipment (Chitnis 2012 [96]). Only two of the studies (Borer 2011 [101], Chitnis 2012 [96]) assessed compliance with environmental cleaning and disinfection. Chitnis 2012 [96] reported that healthcare workers did not adequately clean and disinfect shared equipment and high-touch surfaces between observations. Where reported, specific cleaning solutions included 1.5-ppm chlorine for environmental disinfection for 10 minutes twice daily and 70% alcohol for computers and monitors (Borer 2011 [101]) and 1 000 ppm sodium dichloroisocyanurate (Cohen 2011 [98]). Two studies were carried out during CKRP outbreaks in acute care hospitals in Israel (Borer 2011 [101], Ciobotaro 2011 [97]); both reported significant decreases in CKRP. A decline in CRE levels was also reported for another study of an outbreak of CKRP in an acute care hospital in Israel (Cohen 2011 [98]). However in this study, the effects were dominated by the success of the cohorting element of the infection control bundle. Chitnis 2012 [96] assessed the effects of weekly reminders of appropriate cleaning practices for frequently touched surfaces, for environmental services staff; the study reported a reduction in CRE, including carbapenemase-producing *K. pneumoniae*, *E. coli* and other *Enterobacter* spp., but it was unclear whether this reduction was significant for the phase in which these notes were introduced. The study did, however, report a decrease in the number of newly detected cases, including cases transferred from surrounding hospitals. None of the studies examined the effects of environmental cleaning/disinfection in isolation from other infection control measures.

In summary, there is evidence to suggest that environmental cleaning/disinfection is effective for limiting and preventing the spread of CRE (evidence level ++).

6.5.14 Staff education

The original ECDC 2011 review included three studies [81,84,85] which reported that staff education, as part of a multi-faceted infection control bundle, appeared to be beneficial with respect to the control of CPE.

In this updated 2013 review, three additional studies (Borer 2011 [101], Chitnis 2012 [96], and Ciobotaro 2011 [97]) which included staff education as part of a bundle of infection control measures were found. None of the studies assessed attendance at educational sessions or assessed the effects of staff education in isolation from other infection control measures. All three studies reported significant reductions in CPE. Educational activities focussed on hand hygiene (Borer 2011 [101], Chitnis 2012 [96]), concepts related to CKRP outbreaks (Borer 2011 [101]) and isolation procedures (Ciobotaro 2011 [97], Chitnis 2012 [96]).

In summary, there is evidence to suggest that staff education including information on hand hygiene, isolation procedures and CPE outbreaks in general is effective for limiting and preventing the spread of CPE (evidence level ++).

6.5.15 Case notification and record flagging

The original ECDC review included two studies [83,86] which concluded that internal reporting and external notification of new CPE patients – as part of a multi-faceted infection control bundle – is effective with respect to the control of CPE.

This updated review found an additional three studies (Borer 2011 [101], Ciobotaro 2011 [97], Cohen 2011 [98]) which included case notification as part of an infection control bundle. None of the studies assessed compliance with this specific intervention or the effects of the intervention in isolation from other infection control measures in the bundle. Procedures included flagging of computerised records for high-risk patients on admission (Borer 2011 [101], Ciobotaro 2011 [97]) and previous cases on readmission (Cohen 2011 [98], Ciobotaro 2011 [97]). All three studies were carried out during outbreaks in acute care hospitals in Israel. Two reported reductions in CRKP (Borer 2011 [101], Cohen 2011 [98]), and one in CRKP, including KPC-3-producing isolates (Ciobotaro 2011 [97]). One of the studies (Cohen 2011 [98]) introduced bundles of interventions in phases, but although significant reductions in CRKP were reported, the interventions were dominated by the cohorting element of the infection control bundle.

In summary, there is evidence to suggest that case notification is effective for limiting and preventing the spread of CPE (evidence level ++).

6.5.16 Other infection control measures

The effectiveness of other infection control measures was only supported by very limited evidence, for example visitor education [101], assigned patient transport [101], and dedicated shared equipment [96]. However, further research is needed before recommendations can be made.

7 Discussion

Building on the findings of the previous ECDC risk assessment [1], this systematic review sought to provide an up-to-date summary of the best available evidence regarding the use of interventions to control the transmission and spread of CPE through patient transfer between healthcare facilities, with special emphasis on cross-border transfer. Given the lack of interventions specifically targeting cross-border transfer of patients, this review also included studies that assess infection control measures aimed at preventing CPE transmission both within and between healthcare settings of any type.

7.1 Summary of main findings

Six out of 50 included studies, were selected to represent the best available evidence and were analysed further. Most studies were based in Israel, and all except one US-based study were conducted in areas where CPE was endemic, including one study from Greece. Four of the six studies were outbreak studies. Four studies were based on data from acute care hospitals, one from acute care hospitals and LTCFs, and one from an LCTF. All six studies appeared to include adult populations. The overall quality of the six studies included in the analysis was at best moderate. No controlled study was identified. All studies used a quasi-experimental/before-and-after design, which is known to have inherent methodological problems, limiting the reliability of their findings.

All studies described multi-faceted interventions. Three of the studies introduced infection control measures in phases, some of which only included the introduction of one new measure. All of the studies assessed compliance with the infection control measures to some extent, though in some cases the findings were unclear or not fully reported for all components in the infection control bundle. Some studies reported mixed results for compliance; for example, one reported poor compliance for hand hygiene and inadequate cleaning of medical equipment, but better compliance for contact precautions. Often it was unclear at which stage of the study compliance was measured. In one study, compliance with hand hygiene improved during the study period but was still less than optimal. Three studies assessed the effects of introducing a bundle of interventions, which made it difficult to determine the effectiveness of individual measures. However, these studies all reported beneficial effects for infection control, with two studies reporting significant decreases in the incidence of CRKP.

The quality of the studies and the use of multi-faceted infection control measures hampered the interpretation of the data. There was no specific evidence on transmission of CPE during cross-border transfer. However, two studies included in this 2013 update included patients transferred between hospitals in the surrounding area. There was evidence to suggest that the following infection control measures were effective for the prevention and control of the reported types of CPE: dedicated nursing or other types of dedicated care by staff members(six studies); contact precautions (six studies); hand hygiene (five studies); active screening on admission to specific ward/unit (four studies); active surveillance during outbreak (four studies); patient isolation (four studies); nursing (or staff) cohorting (four studies); environmental cleaning (four studies); staff education (three studies); active screening on admission to hospital (three studies); case notification and record flagging (two studies); and contact tracing (two studies).

Limited evidence was identified in this updated review (2013) for the following infection control measures, which were included in the previous 2011 ECDC risk assessment: pre-emptive isolation on admission (one study); and antibiotic formulary change (one study). No new evidence for ward or ICU closure and antiseptic bathing was identified in this review, though there was evidence in the original 2011 ECDC risk assessment report.

7.2 Comparisons with other research findings

No other systematic review which specifically sought to assess the effectiveness of infection control interventions to control the spread of CPE, with the exception of the previous 2011 ECDC risk assessment [1], could be identified. Kramme 2009 [102] carried out a systematic review of infection control measures taken to control outbreaks with multidrug-resistant gram-negative bacteria including ESBL-E (but not CPE). This review was only published as an abstract and few details are available; 27 articles (published between 2000 and 2009) were included, describing the use of infection control measures in 25 outbreaks. The authors highlighted the lack of controlled studies and concluded that the most commonly used infection control measures were: environmental decontamination of ICUs (56%), active surveillance for colonisation (67%), educational programmes for the staff (37%), single or cohort isolation (59%), and antimicrobial use recommendations (11%).

Although numerous websites and publications mention methods for the control of CPE transmission, only a small number of recently published guidelines/guidance documents specifically refer to infection control measures for the prevention of CPE transmission [1,74-76]. In 2014, ECDC published an online directly which contains a compilation

of all currently available guidance documents for the prevention and control of carbapenemase-resistant Enterobacteriaceae [103]

Studies of measures to control other MDROs, such as ESBL-E, may also be relevant for the control of CPE, given the similarities of the involved bacteria, the transmission sources and routes. Therefore, ECDC commissioned a related systematic review [104] which also provided relevant information regarding potential infection control measures, although this review was also subject to considerable limitations with respect to the quantity and quality of available evidence. Similarly, guidelines on infection control measures published for MDROs and CPE may also offer some relevant advice for the control of ESBL-E.

Guidelines for the control of MDROs published by the Healthcare Infection Control Practices Advisory Committee (HICPAC) and the US Centers for Disease Control and Prevention (CDC) [74] in 2006 identified other infection control measures that were not identified in this ECDC review, such as the use of feedback on changes in prevalence, incidence and problem assessments as well as educational interventions for healthcare professionals and workers. Environmental cleaning, particularly in rooms previously occupied by patients on contact precautions, was also recommended, although this ECDC review did not find any evidence to support this. HICPAC also recommended that colonised or infected patients should be considered for additional measures such as the use of environmental cultures, weekly point prevalence culture surveys, and consultations with experts regarding the potential use of patient decolonisation. Ward closure was also recommended as an option to allow for environmental cleaning and assessment.

7.3 Strengths, limitations and uncertainties

This review has sought to identify and summarise the findings from the best available evidence in this topic area.

The strengths of the review include the adherence to accepted rigorous standards for the conduct of systematic reviews, the close involvement and advice of a topic expert from ECDC, and the use of extensive literature searches to identify relevant data. In order to not miss any relevant data, these searches were not limited by language or outcome. This was of particular concern because it was not always apparent from the title/abstract of the studies whether a study contained relevant data for infection control measures to control CPE transmission. However, when screening the titles/abstracts for inclusion in the review, full articles were ordered for further confirmation when there were doubts about relevance.

The methodological quality of studies often limits the scientific value of a systematic review. In this review, we sought to limit our synthesis to those studies considered to represent the best available evidence. However, studies conducted during an outbreak often employ methodologies which are ineffective in assessing the effectiveness of the introduced infection control measures. Controlled studies, which are generally considered to represent a higher level of evidence, could not be found. The majority of the studies used designs where the incidence/prevalence of CPE was assessed before, during and after the implementation of an intervention. This type of study design is subject to a number of biases, including the risk of confounding. The studies also investigated bundles of interventions introduced at a single time-point or cumulatively over a period of time, which precluded any assessment of the contribution of individual components. In some cases, interventions were introduced in phases and involved the addition of a single new measure at each time-point. However, it was difficult to determine whether the observed beneficial effects were solely due to the addition of the new measure or improvements over time. Similarly, only infection control measures that changed between the pre- to post-intervention periods were considered to be associated with changes in the level of transmission or spread of CPE.

It was often difficult to determine the factors responsible for the observed effects due to the poor reporting standards of many of the studies and the fact that interventions were often part of a bundle of measures and could therefore not be examined in isolation. In addition, compliance was poorly reported.

External circumstances may also have played a role in the compliance and performance of any of the infection control measures, e.g. an improvement in compliance can be due to the presence of a known observer ('Hawthorne effect' or 'observer effect'), a well-documented effect for infection control measures, e.g. hand hygiene [105,106].

The studies discussed in this review were heterogeneous, particularly with respect to populations, interventions, outcomes and their assessment methods, precluding quantitative analysis. The analysis was further hampered by the poor reporting quality of many of the studies despite the fact that reporting guidelines were readily available, e.g. the 'Outbreak reports and intervention studies of nosocomial infection' (ORION) statement [4]. In particular, interventions, outcomes, and outcome assessment methods (i.e. laboratory tests and tests for the detection of the specific types of carbapenemases) were poorly described in many of the studies. The infection control measures applied in the examined studies were often chosen opportunistically, i.e. based on 'popularity', and may not always represent the most effective measures available.

7.4 Recommendations for further research

Based on the findings of this systematic review, the following recommendations are suggested:

- Further research on the following interventional components:
  dedicated nursing or other types of care by dedicated staff, contact precautions, hand hygiene, active screening on admission to specific ward/unit, active surveillance during outbreak, patient isolation, nursing (or staff) cohorting, environmental cleaning, staff education, active screening on admission to hospital, case notification and record flagging, contact tracing, pre-emptive isolation on admission, antibiotic formulary change, ward or ICU closure, and antiseptic bathing.
- Assessment on individual infection control measures in isolation rather than as part of a bundle of interventions.
  If this is not possible, the phased introduction of individual measures over time is preferable to the use of intervention bundles.
- Trials with concurrent controls to avoid recognised biases.
  Studies in endemic areas offer the option to assess the effectiveness of newly introduced individual infection control measures in comparison with standard measures. Future systematic reviews in this topic area would benefit from the results of these studies.
- Reports should be produced in accordance with the ORION statement (description of interventions, outcome assessment, bacterial types, and patient populations).

7.5 Expert meeting

The findings of this review were presented and discussed at a meeting of infection control experts held at ECDC in Stockholm on 30 and 31 January 2014. Representatives from France, Germany, Hungary, Ireland, Italy, Latvia, Malta, the Netherlands, Norway, Spain, the USA and the United Kingdom attended the meeting.

The meeting was held in order to develop ECDC guidance on control measures for the cross-border transmission of MDROs.

During the meeting, participants identified a number of additional studies with potentially relevant data, which were then assessed to determine whether they met the criteria for inclusion in this review (see Appendix 9, available on request).

8 Conclusions

- As stated in the 2011 ECDC risk assessment, there is no evidence of infection control measures to specifically prevent the transmission of CPE during cross-border transfer. Two studies included in this updated review (2013) included patients transferred between hospitals in the same region. From these studies, there is evidence that infection control measures were effective in reducing imported CPE.
- The findings from this updated review confirm and extend the findings from the 2011 ECDC risk assessment in that the evidence for the effectiveness of infection control measures comes only from observational studies reporting infection control measures in 'care bundles' (evidence level ++). This evidence is limited by the lack of data from controlled studies reporting single infection control measures.
- As in the 2011 ECDC risk assessment, evidence from outbreak reports in acute care settings was identified in this updated review for the effectiveness of the early implementation of active surveillance by rectal screening for CPE carriage on hospital admission, admission to specific wards/units, and for surveillance during outbreaks (evidence level ++).
- As in the 2011 ECDC risk assessment, evidence was identified in this 2013 review for the effectiveness of pre-emptive isolation on admission, dedicated nursing or other types of dedicated care by staff members, contact precautions (gloves and gowns) (evidence level ++).
- In this review, evidence was identified for the effectiveness of the following infection control measures: patient cohorting, hand hygiene, patient isolation, nursing (or staff) cohorting (similar to dedicated nursing), environmental cleaning, staff education, case notification/flagging, contact tracing and antibiotic restriction (evidence level ++).
- Evidence for the effectiveness of ward or ICU closure remains available from the original 2011 ECDC risk assessment. No new evidence for these was identified in this updated review.
- Other infection control measures may also be effective, but the evidence supporting their effectiveness is less clear due to a lack of data.
- The best available evidence for the effectiveness of interventions derived from this review and the 2011 ECDC risk assessment comes from data reported from observational studies which, for the most part, include interventions that are part of a bundle of measures, making the effectiveness of each measure less clear. It would, therefore, be necessary to strive for better designed and reported studies that provide evidence for the benefit and harm of infection control measures for the prevention and control of CPE.

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Appendix 1. Search strategies

EMBASE (OvidSP): 2010/08-2013/07/15
Searched 16 July 2013

1 carbapenemase/ or carbapenemase$.ti,ab,ot. (2075)
2 ((carbapenem$ or klebsiella) adj3 (produc$ or secret$ or resist$ or emit$ or generat$ or block$ or immun$ or antagoni$ or "not susceptib$" or unsusceptib$ or un-susceptib$ or non-suscepti$ or non-suscepti$)).ti,ab,ot,hw. (5810)
3 (kpc or vim or mbl or oxa or oxacillinase or oxa48 or metallo-beta-lactamase or "metallo-b-lactamase" or NDM$).ti,ab,ot. (14382)
4 or/1-3 (18733)
5 enterobacteriaceae/ or exp citrobacter/ or exp enterobacter/ or exp escherichia/ or exp hafnia/ or exp klebsiella/ or exp kluyvera/ or exp morganella/ or exp proteus/ or exp providencia/ or exp serratia/ (333528)
6 enterobacteriaceae infection/ or exp escherichia coli infection/ or exp klebsiella infection/ or exp proteus infection/ or exp serratia infection/ (7417)
7 (enterobacter$ or entero-bacter$ or klebsiella or citro-bact$ or citrobact$ or escherichia or hafnia or morganell$ or proteus or serratia or "e coli" or "e.coli").ti,ab,ot. (307020)
8 (kluyvera or providencia or "E.aerogenes" or "e aerogenes" or "k.oxytoca" or "k oxytoca" or "k pneumonia$" or "k.pneumonia$" or "e cloacae" or "e.cloacae").ti,ab,ot. (9164)
9 or/5-8 (407156)
10 4 and 9 (5899)
11 (CPE or CPEs or CRE or CREs or CNSE).ti,ab,ot. (19007)
12 10 or 11 (24796)
13 ((CP or CR) adj2 (enterobacter$ or entero-bacter$)).ti,ab,ot. (16)
14 12 or 13 (24802)
15 infection control/ or infection prevention/ or soap/ or exp face mask/ or mask/ or surgical mask/ or cross infection/pc (113929)
16 hand washing/ or antisepsis/ or mandatory testing/ (11788)
17 protective clothing/ (9631)
18 hospital hygiene/ (2031)
19 (Infection$ adj2 (control$ or prevention or prophyla$)).ti,ab,ot. (32360)
20 (handwash$ or handscrub$ or handrub$).ti,ab,ot. (1680)
21 ((hand or hands) adj2 (wash$ or clean$ or sanit$ or scrub$ or hygien$ or steril$ or gel or gels or sanitiz$ or sanitis$)).ti,ab,ot. (6300)
22 (soap$ or detergent$ or antisepsis or antiseptic$ or anti-septic$ or anti-sepsis or dis-infect$ or disinfect$ or decontamin$ or de-contamin$ or decoloni$ or de-coloni$).ti,ab,ot. (81856)
23 (alcohol adj3 (gel or gels or wash$ or hand-rub$)).ti,ab,ot. (985)
24 (protective cloth$ or protective$ equipment$ or PPE or glove$ or gown$ or facemask$ or faceshield$ or mask$ or face shield$ or apron$ or face mask$).ti,ab,ot. (77577)
25 (barrier$ adj2 (nurs$ or precaution$)).ti,ab,ot. (875)
26 ((nurs$ or patient$ or inpatient$) adj2 (separat$ or isolat$ or segrat$)).ti,ab,ot. (32477)
27 (cohorted or cohorting or quarantin$ or "cohort nursing").ti,ab,ot. (3408)
28 ((ward or wards or hospital$ or unit or units or ICU or ICUs or HDU or HDUs or PICU or PICUs or SCBU or SCBUs or CCU or CCUs or NICU or NICUs or ITU or ITUs or er or ers or "emergency room" or "emergency rooms" or "emergency department" or "emergency departments" or "casualty department" or "casualty departments" or "accident and emergency" or "A&E" or "A & E" or centre or centres or center or centers or clinic or clinics or infirmary or infirmaries or facility or facilities) adj4 (hygien$ or clean$ or disinfect$ or dis-infect$ or sanitis$ or sanitiz$ or sanita$ or steril$ or decontamin$ or de-contamin$)).ti,ab,ot. (7635)
29 ((antibiotic$ or anti-biotic$ or antimicrobial$ or anti-microbial$) adj2 (class shift or restrict$ or limit$ or reduc$ or minimi$)).ti,ab,ot. (4387)
30 screening/ or feces analysis/ (112051)
31 (screen$ or surveill$ or molecular diagnos$ technique$ or microbiology$ technique$ or "clover leaf" or cloverleaf or hodge or phenylboronic or phenyl-boronic or pcr or edta or pba or chromogen$ or culture medi$ or microbial$ sensitivity$ test$ or "double disk " or breakpoint$).ti,ab,ot. (1163214)
32 ((faeces or feces or faecal$ or fecal$ or rectal$ or rectum or stool or bowel movements$) adj2 (test$ or swab$ or specimen$ or sampl$ or screen$)).ti,ab,ot. (29378)
33 (carriage$ or coloniz$ or colonis$).ti,ab,ot. (73443)
34 or/15-33 (1560630)
35 14 and 34 (5143)
36 enterobacteriaceae infection/pc, dm or exp escherichia coli infection/pc, dm or exp klebsiella infection/pc, dm or exp proteus infection/pc, dm or exp serratia infection/pc, dm (441)
37 35 or 36 (5545)
38 (201008$ or 2011$ or 2012$ or 2013$).dd. (3487389)
39 37 and 38 (2620)
40 (2010$ or 2011$ or 2012$ or 2013$).em. (4063525)
41 37 and 40 (2765)
42 39 or 41 (2953)

MEDLINE (OvidSP): 2010/08-2013/07/15
Searched 16 July 2013

1 carbapenemase$.ti,ab,ot. (1256)
2 ((carbapenem$ or klebsiella) adj3 (produc$ or secret$ or resist$ or emit$ or generat$ or block$ or immun$ or antagoni$ or "not susceptib$" or unsusceptib$ or un-susceptib$ or non-suscepti$ or non-suscepti$)).ti,ab,ot,hw. (4230)
3 (kpc or vim or mbl or oxa or oxacillinase or oxa48 or metallo-beta-lactamase or "metallo-b-lactamase" or NDM$).ti,ab,ot. (10687)
4 or/1-3 (13756)
5 enterobacteriaceae/ or exp citrobacter/ or exp enterobacter/ or exp escherichia/ or exp hafnia/ or exp klebsiella/ or kluyvera/ or exp morganella/ or exp proteus/ or providencia/ or exp serratia/ (275553)
6 enterobacteriaceae infections/ or exp escherichia coli infections/ or exp klebsiella infections/ or proteus infections/ or serratia infections/ (39635)
7 (enterobacter$ or entero-bacter$ or klebsiella or citro-bact$ or citrobact$ or escherichia or hafnia or morganell$ or proteus or serratia or "e coli" or "e.coli").ti,ab,ot. (281581)
8 (kluyvera or providencia or "E.aerogenes" or "e aerogenes" or "k.oxytoca" or "k oxytoca" or "k pneumonia$" or "k.pneumonia$" or "e cloacae" or "e.cloacae").ti,ab,ot. (7047)
9 or/5-8 (373193)

10 4 and 9 (4347)
11 (CPE or CPEs or CRE or CREs or CNSE).ti,ab,ot. (15657)
12 10 or 11 (19957)
13 ((CP or CR) adj2 (enterobacter$ or entero-bacter$)).ti,ab,ot. (4)
14 12 or 13 (19961)
15 infection control/ or patient isolation/ or quarantine/ or soaps/ or masks/ or cross infection/pc (40935)
16 hand disinfection/ or antisepsis/ or mandatory testing/ (8283)
17 protective clothing/ or gloves, protective/ (6027)
18 (Infection$ adj2 (control$ or prevention or prophyla$)).ti,ab,ot. (25155)
19 (handwash$ or handscrub$ or handrub$).ti,ab,ot. (1443)
20 ((hand or hands) adj2 (wash$ or clean$ or sanit$ or scrub$ or hygien$ or steril$ or gel or gels or sanitiz$ or sanitis$)).ti,ab,ot. (4521)
21 (soap$ or detergent$ or antisepsis or antiseptic$ or anti-septic$ or anti-sepsis or dis-infect$ or disinfect$ or decontamin$ or de-contamin$ or decoloni$ or de-coloni$).ti,ab,ot. (66741)
22 (alcohol adj3 (gel or gels or wash$ or hand-rub$)).ti,ab,ot. (692)
23 (protective cloth$ or protective$ equipment$ or PPE or glove$ or gown$ or facemask$ or faceshield$ or mask$ or face shield$ or apron$ or face mask$).ti,ab,ot. (62324)
24 (barrier$ adj2 (nurs$ or precaution$)).ti,ab,ot. (703)
25 ((nurs$ or patient$ or inpatient$) adj2 (separat$ or isolat$ or segrat$)).ti,ab,ot. (25058)
26 (cohorted or cohorting or quarantin$ or "cohort nursing").ti,ab,ot. (2877)
27 ((ward or wards or hospital$ or unit or units or ICU or ICUs or HDU or HDUs or PICU or PICUs or SCBU or SCBUs or CCU or CCUs or NICU or NICUs or ITU or ITUs or er or ers or "emergency room" or "emergency rooms" or "emergency department" or "emergency departments" or "casualty department" or "casualty departments" or "accident and emergency" or "A&E" or "A & E" or centre or centres or center or centers or clinic or clinics or infirmary or infirmaries or facility or facilities) adj4 (hygien$ or clean$ or disinfect$ or dis-infect$ or sanitis$ or sanitiz$ or sanita$ or steril$ or decontamin$ or de-contamin$)).ti,ab,ot. (5327)
28 ((antibiotic$ or anti-biotic$ or antimicrobial$ or anti-microbial$) adj2 (class shift or restrict$ or limit$ or reduc$ or minimi$)).ti,ab,ot. (3417)
29 Mass Screening/ (81834)
30 (screen$ or surveill$ or molecular diagnos$ technique$ or microbiology$ technique$ or "clover leaf" or cloverleaf or hodge or phenylboronic or phenyl-boronic or pcr or edta or pba or chromogen$ or culture medi$ or microbial$ sensitivity$ test$ or "double disk " or breakpoint$).ti,ab,ot. (911088)
31 ((faeces or feces or faecal$ or fecal$ or rectal$ or rectum or stool or bowel movements$) adj2 (test$ or swab$ or specimen$ or sampl$ or screen$)).ti,ab,ot. (25323)
32 (carriage$ or coloniz$ or colonis$).ti,ab,ot. (64566)
33 or/15-32 (1202476)
34 14 and 33 (3339)
35 enterobacteriaceae infections/pc, dm or exp escherichia coli infections/pc or exp klebsiella infections/pc or proteus infections/pc or serratia infections/pc (2887)
36 or/34-35 (6143)
37 (201008$ or 201009$ or 20101$ or 2011$ or 2012$ or 2013$).ed,dc. or (2010$ or 2011$ or 2012$ or 2013$).yr. (2886514)
38 36 and 37 (1736)

MEDLINE In-Process Citations (OvidSP): up to 2013/07/15
MEDLINE Daily Update (OvidSP): up to 2013/07/15
Searched 16 July 2013

1 carbapenemase$.ti,ab,ot. (172)
2 ((carbapenem$ or klebsiella) adj3 (produc$ or secret$ or resist$ or emit$ or generat$ or block$ or immun$ or antagoni$ or "not susceptib$" or unsusceptib$ or un-susceptib$ or non-suscepti$ or non-suscepti$)).ti,ab,ot,hw. (385)
3 (kpc or vim or mbl or oxa or oxacillinase or oxa48 or metallo-beta-lactamase or "metallo-b-lactamase" or NDM$).ti,ab,ot. (982)
4 or/1-3 (1254)
5 enterobacteriaceae/ or exp citrobacter/ or exp enterobacter/ or exp escherichia/ or exp hafnia/ or exp klebsiella/ or kluyvera/ or exp morganella/ or exp proteus/ or providencia/ or exp serratia/ (200)
6 enterobacteriaceae infections/ or exp escherichia coli infections/ or exp klebsiella infections/ or proteus infections/ or serratia infections/ (43)
7 (enterobacter$ or entero-bacter$ or klebsiella or citro-bact$ or citrobact$ or escherichia or hafnia or morganell$ or proteus or serratia or "e coli" or "e.coli").ti,ab,ot. (9922)
8 (kluyvera or providencia or "E.aerogenes" or "e aerogenes" or "k.oxytoca" or "k oxytoca" or "k pneumonia$" or "k.pneumonia$" or "e cloacae" or "e.cloacae").ti,ab,ot. (373)
9 or/5-8 (9996)
10 4 and 9 (377)
11 (CPE or CPEs or CRE or CREs or CNSE).ti,ab,ot. (851)
12 10 or 11 (1209)
13 ((CP or CR) adj2 (enterobacter$ or entero-bacter$)).ti,ab,ot. (0)
14 12 or 13 (1209)
15 infection control/ or patient isolation/ or quarantine/ or soaps/ or masks/ or cross infection/pc (43)
16 hand disinfection/ or antisepsis/ or mandatory testing/ (10)
17 protective clothing/ or gloves, protective/ (14)
18 (Infection$ adj2 (control$ or prevention or prophyla$)).ti,ab,ot. (1620)
19 (handwash$ or handscrub$ or handrub$).ti,ab,ot. (44)
20 ((hand or hands) adj2 (wash$ or clean$ or sanit$ or scrub$ or hygien$ or steril$ or gel or gels or sanitiz$ or sanitis$)).ti,ab,ot. (387)
21 (soap$ or detergent$ or antisepsis or antiseptic$ or anti-septic$ or anti-sepsis or dis-infect$ or disinfect$ or decontamin$ or de-contamin$ or decoloni$ or de-coloni$).ti,ab,ot. (3833)
22 (alcohol adj3 (gel or gels or wash$ or hand-rub$)).ti,ab,ot. (69)
23 (protective cloth$ or protective$ equipment$ or PPE or glove$ or gown$ or facemask$ or faceshield$ or mask$ or face shield$ or apron$ or face mask$).ti,ab,ot. (5526)
24 (barrier$ adj2 (nurs$ or precaution$)).ti,ab,ot. (46)
25 ((nurs$ or patient$ or inpatient$) adj2 (separat$ or isolat$ or segrat$)).ti,ab,ot. (1030)
26 (cohorted or cohorting or quarantin$ or "cohort nursing").ti,ab,ot. (309)
27 ((ward or wards or hospital$ or unit or units or ICU or ICUs or HDU or HDUs or PICU or PICUs or SCBU or SCBUs or CCU or CCUs or NICU or NICUs or ITU or ITUs or er or ers or "emergency room" or "emergency rooms" or "emergency department" or "emergency departments" or "casualty department" or "casualty departments" or "accident and emergency" or "A&E" or "A & E" or centre or centres or center or centers or clinic or clinics or infirmary or infirmaries or facility or facilities) adj4 (hygien$ or clean$ or disinfect$ or dis-infect$ or sanitis$ or sanitiz$ or sanita$ or steril$ or decontamin$ or de-contamin$)).ti,ab,ot. (336)

28 ((antibiotic$ or anti-biotic$ or antimicrobial$ or anti-microbial$) adj2 (class shift or restrict$ or limit$ or reduc$ or minimi$)).ti,ab,ot. (272)
29 Mass Screening/ (95)
30 (screen$ or surveill$ or molecular diagnos$ technique$ or microbiology$ technique$ or "clover leaf" or cloverleaf or hodge or phenylboronic or phenyl-boronic or pcr or edta or pba or chromogen$ or culture medi$ or microbial$ sensitivity$ test$ or "double disk " or breakpoint$).ti,ab,ot. (59528)
31 ((faeces or feces or faecal$ or fecal$ or rectal$ or rectum or stool or bowel movements$) adj2 (test$ or swab$ or specimen$ or sampl$ or screen$)).ti,ab,ot. (1424)
32 (carriage$ or coloniz$ or colonis$).ti,ab,ot. (4386)
33 or/15-32 (75520)
34 14 and 33 (292)
35 enterobacteriaceae infections/pc, dm or exp escherichia coli infections/pc or exp klebsiella infections/pc or proteus infections/pc or serratia infections/pc (4)
36 or/34-35 (296)

Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley). Issue 6: 2013
Health Technology Assessment Database (HTA) (Wiley). Issue 2: 2013
Searched 16 July 2013
http://onlinelibrary.wiley.com/cochranelibrary/search/advanced/shared/searches/13822216124175980920

#1 carbapenemase*:ti,ab 1
#2 ((carbapenem* or klebsiella) near/3 (produc* or secret* or resist* or emit* or generat* or block* or immun* or antagoni* or "not susceptib*" or unsusceptib* or un-susceptib* or non-suscepti* or non-suscepti*)):ti,ab,kw 49
#3 (kpc or vim or mbl or oxa or oxacillinase or oxa48 or metallo-beta-lactamase or "metallo-b-lactamase" or NDM*):ti,ab 199
#4 #1 or #2 or #3 249
#5 MeSH descriptor: [Enterobacteriaceae] this term only 157
#6 MeSH descriptor: [Citrobacter] explode all trees 6
#7 MeSH descriptor: [Enterobacter] explode all trees 28
#8 MeSH descriptor: [Enterobacteriaceae Infections] this term only 108
#9 MeSH descriptor: [Escherichia coli Infections] explode all trees 331
#10 MeSH descriptor: [Klebsiella Infections] explode all trees 68
#11 MeSH descriptor: [Proteus Infections] this term only 51
#12 MeSH descriptor: [Serratia Infections] this term only 2
#13 MeSH descriptor: [Escherichia] explode all trees 533
#14 MeSH descriptor: [Hafnia] explode all trees 0
#15 MeSH descriptor: [Klebsiella] explode all trees 123
#16 MeSH descriptor: [Kluyvera] this term only 0
#17 MeSH descriptor: [Morganella] explode all trees 1
#18 MeSH descriptor: [Proteus] explode all trees 72
#19 MeSH descriptor: [Providencia] this term only 2
#20 MeSH descriptor: [Serratia] explode all trees 17
#21 (enterobacter* or entero-bacter* or klebsiella or citro-bact* or citrobact* or escherichia or hafnia or morganell* or proteus or serratia or "e coli" or "e.coli") 2648
#22 (kluyvera or providencia or "E.aerogenes" or "e aerogenes" or "k.oxytoca" or "k oxytoca" or "k pneumonia*" or "k.pneumonia*" or "e cloacae" or "e.cloacae") 79
#23 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 2658
#24 #4 and #23 47
#25 (CPE or CPEs or CRE or CREs or CNSE):ti,ab 76
#26 #24 or #25 123
#27 ((CP or CR) near/2 (enterobacter* or entero-bacter*)):ti,ab 0
#28 #26 or #27 from 2010 to 2013 16

The CENTRAL search retrieved 13 references.
The HTA search retrieved 1 reference.

INAHTA (International Network of Agencies for Health Technology Assessment): up to 2013/07/16
http://www.inahta.org/Search2/?pub=1
Searched 16 July 2013

Search term	Results
Carbapen	0
carbapenem	0
carbapenemase	0
carbapenemases	0
CPE	0
CPEs	0
NDM	0
KPC	0
VIM	0
MBL	0
OXA	0
Oxacillinase	0
OXA48	0
Metallo beta lactamase	1
CRE	8
CREs	0
CNSE	0

Search term	Results
Enterobacter	0
Enterobacteria	0
Enterobacteriaceae	0
Citrobacter	0
Escherichia	1
Hafnia	0
Klebsiella	0
Kluyvera	0
Morganella	0
Proteus	0
Providencia	0
Serratia	0
Total	**10**

Appendix 2. Quality assessment criteria, Downs & Black

The following quality assessment criteria developed by Downs & Black [93] were used to assess the methodological quality of each of the seven studies included in the analysis section of the report.

Each of the studies was assessed individually and graded using the following responses for each of the 27 Downs & Black criteria:

- Yes – yes, criterion was met
- No – no, criterion was not met
- Unclear/NR – insufficient information to make a judgement
- NA – not applicable (i.e. the design or topic area meant that this criterion was not relevant to assess)

In addition, text to support the judgements was recorded where relevant.

Criterion number	Quality assessment question assessed
1	Is the hypothesis/aim/objective of the study clearly described?
2	Are the main outcomes to be measured clearly described in the introduction or methods section?
3	Are the characteristics of the patients included in the study clearly described?
4	Are the interventions of interest clearly described?
5	Are the distributions of principal confounders in each group of subjects to be compared clearly described?
6	Are the main findings of the study clearly described?
7	Does the study provide estimates of the random variability in the data for the main outcomes?
8	Have all important adverse events that may be a consequence of the intervention been reported?
9	Have the characteristics of patients lost to follow-up been described?
10	Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value <0.001?
11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
12	Were those subjects who were prepared to participate, representative of the entire population from which they were recruited?
13	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?
14	Was an attempt made to blind study subjects to the intervention they have received?
15	Was an attempt made to blind those measuring the main outcomes of the intervention?
16	If any of the results of the study were based on 'data dredging', was this made clear?
17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?
18	Were the statistical tests used to assess the main outcomes appropriate?
19	Was compliance with the intervention/s reliable?
20	Were the main outcome measures used accurate (valid and reliable)?
21	Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?
22	Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?
23	Were study subjects randomised to intervention groups? (NA if not comparative study)
24	Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? (NA if not comparative study)
25	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?
26	Were losses of patients to follow-up taken into account?
27	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?

Appendix 3. List of studies not meeting inclusion criteria and excluded from the review at the full paper screening stage; reasons for exclusion

List of studies excluded at full paper screening stage; excluded studies do not meet the inclusion criteria for the review for one or more reasons. A total of 56 studies was excluded (48 studies + 7 duplicates; 1 unobtainable).

A. Excluded studies which do not meet criteria for population/intervention/outcome (48 studies)

1. Kaiser RM, Castanheira M, Jones RN, Tenover F, Lynfield R. Trends in Klebsiella pneumoniae carbapenemase-positive K. Pneumoniae in US hospitals: report from the 2007-2009 SENTRY Antimicrobial Surveillance Program. Diagn Microbiol Infect Dis. 2013;76(3):356-60. **Reason for exclusion:** Prevalence of antimicrobial data

2. Gutierrez C, Labarca J, Roman JC, Sanhueza F, Moraga M, Wozniak A, et al. Surveillance of carbapenem-resistant Enterobacteria in stool cultures in a university hospital in Santiago, Chile. Rev Chilena Infectol. 2013;30(1):103-6. **Reason for exclusion:** Surveillance not infection control

3. Savard P, Carroll KC, Wilson LE, Perl TM. The challenges of carbapenemase-producing Enterobacteriaceae and infection prevention: protecting patients in the chaos. Infect Control Hosp Epidemiol. 2013;34(7):730-9. **Reason for exclusion:** Opinion paper

4. Fabbri G, Panico M, Dallolio L, Suzzi R, Ciccia M, Sandri F, et al. Outbreak of ampicillin/piperacillin-resistant Klebsiella pneumoniae in a neonatal intensive care unit (NICU): investigation and control measures. International Journal of Environmental Research and Public Health. 2013;10(3):808-15. **Reason for exclusion:** Not looking at effects of intervention; no transmission results

5. Burns K, Morris D, Murchan S, Cunney R, Smyth E, Power M, et al. Carbapenemase-producing Enterobacteriaceae in Irish critical care units: results of a pilot prevalence survey, June 2011. J Hosp Infect. 2013;83(1):71-3. **Reason for exclusion:** Prevalence survey; no intervention identified

6. Lowe C, Katz K, McGeer A, Muller MP. Disparity in infection control practices for multidrug-resistant Enterobacteriaceae. Am J Infect Control. 2012;40(9):836-9. **Reason for exclusion:** Survey of infection control measures

7. Balkhy HH, El-Saed A, Al Johani SM, Francis C, Al-Qahtani AA, Al-Ahdal MN, et al. The epidemiology of the first described carbapenem-resistant Klebsiella pneumoniae outbreak in a tertiary care hospital in Saudi Arabia: How far do we go? Eur J Clin Microbiol Infect Dis. 2012;31(8):1901-9. **Reason for exclusion:** No before or after results for intervention.

8. Fournier S, Lepainteur M, Kassis-Chikhani N, Huang M, Brun-Buisson C, Jarlier V. Link between carbapenemase-producing Enterobacteria carriage and cross-border exchanges: eight-year surveillance in a large french multihospitals institution. J Travel Med. 2012;19(5):320-3. **Reason for exclusion:** No intervention reported

9. Landman D, Babu E, Shah N, Kelly P, Olawole O, Backer M, et al. Transmission of carbapenem-resistant pathogens in New York City hospitals: progress and frustration. J Antimicrob Chemother. 2012;67(6):1427-31. **Reason for exclusion:** No intervention identified

10. Sanchez M, Herruzo R, Marban A, Araujo P, Asensio MJ, Leyva F, et al. Risk factors for outbreaks of multidrug-resistant Klebsiella pneumoniae in critical burn patients. Journal of Burn Care and Research. 2012;33(3):386-92. **Reason for exclusion:**

11. Centers for Disease Control and Prevention. Carbapenem-resistant Klebsiella pneumoniae associated with a long-term-care facility - West Virginia, 2009-2011. Ann Emerg Med. 2012;59(5):434-6. **Reason for exclusion:** No intervention; transmission surveillance

12. Cuzon G, Naas T, Demachy MC, Nordmann P. Nosocomial outbreak of Klebsiella pneumoniae harbouring blaKPC-3 in France subsequent to a patient transfer from Italy. Int J Antimicrob Agents. 2012;39(5):448-9. **Reason for exclusion:** Intervention unclear

13. Cuzon G, Naas T, Demachy M, Ittah-Desmeulles H, Nordmann P. Nosocomial outbreak of Klebsiella pneumoniae harbouring blaKPC-3 in France subsequent to a patient transfer from Italy. Presented at 21st ECCMID/27th ICC; 7 - 10 May 2011; Milan: Italy. Clin Microbiol Infect. 2011;17:S169-70. **Reason for exclusion:** Intervention unclear

14. Schaffzin JK, Coronado F, Dumas NB, Root TP, Halse TA, Schoonmaker-Bopp DJ, et al. Public health approach to detection of non-O157 Shiga toxin-producing Escherichia coli: summary of two outbreaks and laboratory procedures. Epidemiol Infect. 2012;140(2):283-9. **Reason for exclusion:** Intervention unclear; monitoring outbreak

15. Saidel-Odes LMD, Polachek HP, Peled NM, Riesenberg KMD, Schlaeffer FMD, Trabelsi YRN, et al. A Randomized, Double-Blind, Placebo-Controlled Trial of Selective Digestive Decontamination Using Oral Gentamicin and Oral Polymyxin E for Eradication of Carbapenem-Resistant Klebsiella pneumoniae Carriage. Infect Control Hosp Epidemiol. 2012;33(1):14-9. **Reason for exclusion:** Comparison of therapeutic options

16. Ben-David D, Masarwa S, Navon-Venezia S, Mishali H, Fridental I, Rubinovitch B, et al. Carbapenem-resistant Klebsiella pneumoniae in post-acute-care facilities in Israel. Infect Control Hosp Epidemiol. 2011;32(9):845-53. **Reason for exclusion:** Prevalence survey

17. Lurio J, Morrison FP, Pichardo M, Berg R, Buck MD, Wu W, et al. Using electronic health record alerts to provide public health situational awareness to clinicians. Journal of the American Medical Informatics Association : JAMIA. 2010;17(2):217-9. **Reason for exclusion:** Not relevant to CPE/CRE

18. Struelens MJ, Monnet DL, Magiorakos AP, Santos O'Connor F, Giesecke J. New Delhi metallo-beta-lactamase 1-producing Enterobacteriaceae: emergence and response in Europe. Euro Surveill. 2010 Nov 18;15(46). **Reason for exclusion:** Systematic review relevant to NDM-1

19. Schweickert B, Noll I, Feig M, Claus H, Abu Sin M, Krause G, et al. Carbapenem-non-susceptibility in Gram negative bacteria: data from the German Antibiotic Resistance Surveillance System (ARS) from 2008-2011. Presented at 64 Jahrestagung der Deutschen Gesellschaft fur Hygiene und Mikrobiologie, DGHM; 30 Sept - 3 Oct 2012; Hamburg: Germany. Int J Med Microbiol. 2012;301(Suppl 1):95. **Reason for exclusion:** Screening; no infection control

20. Jurs U, Huggett S. The handling of multi-resistant Gram-negative bacteria based on daily practical experience. Presented at 64 Jahrestagung der Deutschen Gesellschaft fur Hygiene und Mikrobiologie, DGHM; 30 Sept - 3 Oct 2012; Hamburg: Germany. Int J Med Microbiol. 2012;302(Suppl 1):32. **Reason for exclusion:** Unclear interventions

21. Sauzay C. Management of a patient colonized with a carbapenem-resistant Enterobacteriaceae. Presented at ESCP International Workshop Patients: Infections and the Clinical Pharmacist; 3 May - 1 Jun 2012; Leuven: Belgium. Int J Clin Pharm. 2012;34(5):792. **Reason for exclusion:** Management/guidance

22. De Vos D, Bilocq F, Verbeken G, Pieters T, Dijkshoorn L, Bogaerts P, et al. Thermally injured and Acinetobacter baumannii colonizations/infections during a five-year period at the Brussels Burn Wound Centre. In: 15th International Congress on Infectious Diseases, ICID; 13-16 Jun 2012; Bangkok, Thailand. Int J Infect Dis. 2012;16(Supplement 1):e413. **Reason for exclusion:** Data are only for A. baumannii

23. Sukhorukova M, Savochkina J, Alexandrova I, Timohova A, Edelstein M. First outbreak of carbapenem-resistant OXA-48-producing Klebsiella pneumoniae in Russia. In: 22nd European Congress of Clinical Microbiology and Infectious Diseases; 31 Mar - 3 Apr 2012; London, UK. Clin Microbiol Infect. 2012;18(Suppl s3):750. **Reason for exclusion:** Lack of detail; no relevant data

24. Plachouras D, Papadomichelakis E, Antoniadou A, Armaganidis A, Petrikkos G. Assessment of transmission dynamics of KPC carbapenemase producing Klebsiella pneumoniae in an intensive care unit using a stochastic model. Presented at 22nd European Congress of Clinical Microbiology and Infectious Diseases; 31 Mar - 3 Apr 2012; London: UK. Clin Microbiol Infect. 2012;18(Suppl s3):49. **Reason for exclusion: Lack of data;** intervention unclear

25. De Jong E, Hopman J, Hilkens MGEC, Loeffen FLA, Van Leeuwen WB, Melchers WJ, et al. A prolonged outbreak of an extended-spectrum betalactamase producing Klebsiella pneumoniae (EKP) on an ICU due to contamination of sinks. Presented at 22nd European Congress of Clinical Microbiology and Infectious Diseases; 31 Mar - 3 Apr 2012; London: UK. Clin Microbiol Infect. 2012;18(Suppl s3):14. **Reason for exclusion:** No relevant data (abstract only)

26. Mace M, Leonard A, Thurman D. Resistant organisms: an innovative approach to preventing healthcare transmission. Presented at 39th Annual Educational Conference and International Meeting of the Association for Professionals in Infection Control and Epidemiology, Inc., APIC; 4-6 Jun 2012; San Antonio: TX. Am J Infect Control. 2012;40(5):e99-e100. **Reason for exclusion:** No data for CPE/CRE

27. Balkhy HH, El-Saed A, Al Johani S, Tayeb HT, Al-Qahtani A, Alahdal M, et al. Epidemiology of the first outbreak of carbapenem-resistant Klebsiella pneumoniae in Saudi Arabia. Poster presented at International Conference on Prevention and Infection Control, ICPIC; 29 Jun - 2 Jul 2011; Geneva: Switzerland. BMC Proc. 2011;5(Suppl 6):295. **Reason for exclusion:** Data unclear

28. Anumakonda V, Ramamoorthy M, Murthy RG, Pyda V. Management of multiple pathogens with a bla-new Delhi metallo-carbapenemase gene in a critical care unit: a challenge. Presented at 24th Annual Congress of the European Society of Intensive Care Medicine, ESICM LIVES; 1-5 Oct 2011; Berlin: Germany. Intensive Care Med. 2011;37:S15. **Reason for exclusion: Case study;** No relevant data

29. Halfmann A, Heinzel E, Kaase M, Petit C, Gartner B, Meiser A, et al. Outbreak of Carbapenem resistant Klebsiella pneumoniae in a University Hospital: can MALDI-TOF be helpful for initial epidemiological analysis? Presented at 63 Jahrestagung der Deutschen Gesellschaft fur Hygiene und Mikrobiologie, DGHM; 25-28 Sept 2011; Essen: Germany. Int J Med Microbiol. 2011;301:4. **Reason for exclusion:** Not relevant intervention/comparator

30. Rodriguez-Bano J, Garcia L, Lopez-Cerero L, Lupion C, Alex M, Gonzalez C, et al. Long-term maintenance of very low incidence of nosocomial multidrug-resistant pathogens in a tertiary hospital in Spain. Presented at 21st ECCMID/27th ICC; 7 - 10 May 2011; Milan: Italy. Clin Microbiol Infect. 2011;17:S30. **Reason for exclusion:** no intervention reported

31. Geroulanos S. Prophylaxis from and treatment of multiresistant germ-microepidemics; 35 years of experience. Presented at 5th International Meeting of the Onassis Cardiac Surgery Center; 16-18 Sept 2010; Athens: Greece. Heart Surg Forum. 2010;13:S30. **Reason for exclusion:** No relevant intervention

32. Lowe C, Willey B, O'Shaughnessy A, Lee W, Lum M, Pike K, et al. Outbreak of extended-spectrum beta-lactamase-producing Klebsiella oxytoca infections associated with contaminated handwashing sinks. Emerg Infect Dis. 2012;18(8):1242-7. **Reason for exclusion:** Refers to ESBL

33. Ross B, Witzke O, Kribben A, Heintschel von Heinegg E, Buer J, Gerken G, et al. [Managing EHEC in hospital routine]. Dtsch Med Wochenschr. 2012 May;137(18):933-6. **Reason for exclusion:** No relevant data

34.Centers for Disease C, Prevention. Carbapenem-resistant Klebsiella pneumoniae associated with a long-term-care facility - West Virginia, 2009-2011. MMWR - Morbidity & Mortality Weekly Report. 2011 Oct 21;60(41):1418-20. **Reason for exclusion:** No intervention reported

35. Starlander G, Melhus A. Minor outbreak of extended-spectrum beta-lactamase-producing Klebsiella pneumoniae in an intensive care unit due to a contaminated sink. J Hosp Infect. 2012;82(2):122-4.**Reason for exclusion:** Data not relevant

36. Polilli E, Parruti G, Fazii P, D'Antonio D, Palmieri D, D'Incecco C, et al. Rapidly controlled outbreak of Serratia marcescens infection/colonisations in a neonatal intensive care unit, Pescara General Hospital, Pescara, Italy, April 2011. [Erratum appears in Euro Surveill. 2011;16(27). pii: 19910]. Euro Surveill. 2011;16(24). **Reason for exclusion**: Not relevant to CPE/CRE

37. Mendoza-Guevara L, Castro-Vazquez F, Aguilar-Kitsu A, Morales-Nava A, Rodriguez-Leyva F, Sanchez-Barbosa JL. Amuchina 10% solution, safe antiseptic for preventing infections of exit-site of Tenckhoff catheters, in the pediatric population of a dialysis program. Contrib Nephrol. 2007;154:139-44. **Reason for exclusion:** Population not relevant

38. Laux R, Wirtz S, Huggett S, Ilchmann C. [Relevance of parents as source for contamination of neonates with multiresistant Gram-negative pathogens (MRGN)]. Z Geburtshilfe Neonatol. 2013 Apr;217(2):61-4. **Reason for exclusion:** No results reported after intervention

39. Zimmerman FS, Assous MV, Bdolah-Abram T, Lachish T, Yinnon AM, Wiener-Well Y. Duration of carriage of carbapenem-resistant Enterobacteriaceae following hospital discharge. Am J Infect Control. 2013 Mar;41(3):190-4. **Reason for exclusion:** No intervention described

40. Richter SN, Frasson I, Franchin E, Bergo C, Lavezzo E, Barzon L, et al. KPC-mediated resistance in Klebsiella pneumoniae in two hospitals in Padua, Italy, June 2009-December 2011: massive spreading of a KPC-3-encoding plasmid and involvement of non-intensive care units. Gut Pathog. 2012;4(1):7. **Reason for exclusion:** No intervention

41. Tzouvelekis LS, Markogiannakis A, Psichogiou M, Tassios PT, Daikos GL. Carbapenemases in Klebsiella pneumoniae and other Enterobacteriaceae: An evolving crisis of global dimensions. Clin Microbiol Rev. 2012;25(4):682-707. **Reason for exclusion:** No detail on infection control interventions

42.Zavascki AP, Carvalhaes CG, da Silva GL, Tavares Soares SP, de Alcantara LR, Elias LS, et al. Outbreak of carbapenem-resistant Providencia stuartii in an intensive care unit. Infect Control Hosp Epidemiol. 2012 Jun;33(6):627-30. **Reason for exclusion:** No data pre- or post- intervention

43. Bilavsky E, Schwaber MJ, Carmeli Y. How to stem the tide of carbapenemase-producing enterobacteriaceae?: proactive versus reactive strategies. Curr Opin Infect Dis. 2010 Aug;23(4):327-31. **Reason for exclusion:** Discussion on guidelines

44. Calfee DP. Klebsiella pneumoniae carbapenemase-producing enterobacteriaceae. J Infus Nurs. 2010;33(3):150-4. **Reason for exclusion:** Opinion paper

45. Endimiani A, DePasquale JM, Forero S, Perez F, Hujer AM, Roberts-Pollack D, et al. Emergence of blaKPC-containing Klebsiella pneumoniae in a long-term acute care hospital: A new challenge to our healthcare system. J Antimicrob Chemother. 2009;64(5):1102 10. **Reason for exclusion:** Intervention measures unclear and no clear results data

46. Centers for Disease Control and Prevention. Guidance for control of infections with carbapenem-resistant or carbapenemase-producing Enterobacteriaceae in acute care facilities. MMWR - Morbidity & Mortality Weekly Report. 2009 Mar 20;58(10):256-60. **Reason for exclusion:** No interventions reported

47. Hara GL, Gould I, Endimiani A, Pardo PR, Daikos G, Hsueh P-R, et al. Detection, treatment, and prevention of carbapenemase-producing Enterobacteriaceae: Recommendations from an International Working Group. J Chemother. 2013;25(3):129-40. **Reason for exclusion:** Guidance paper on management of CPE

48. Muugulug T, Bat-Erdene A. Neonatal sepsis outbreak at the first maternity hospital of Ulaanbaatar. Presented at International Conference on Prevention and Infection Control, ICPIC; 29 Jun - 2 Jul 2011; Geneva: Switzerland. BMC Proc. 2011;5(Suppl 6):P96 **Reason for exclusion:** Intervention not clear

B. Excluded: duplicate studies (7 studies)

49. Zagorianou A, Sianou E, Iosifidis E, Dimou V, Protonotariou E, Miyakis S, et al. Microbiological and molecular characteristics of carbapenemase-producing Klebsiella pneumonia endemic in a tertiary Greek hospital during 2004-2010. Euro Surveill. 2012;17(7).

50. Kassis-Chikhani N, Saliba F, Carbonne A, Neuville S, Decre D, Sengelin C, et al. Extended measures for controlling an outbreak of VIM-1 producing imipenem-resistant Klebsiella pneumoniae in a liver transplant centre in France, 2003-2004. Euro Surveill. 2010;15(46).

51. Munoz-Price LS, Hayden MK, Lolans K, Won S, Calvert K, Lin M, et al. Successful control of an outbreak of Klebsiella pneumoniae carbapenemase- producing K. pneumoniae at a long-term acute care hospital. Infect Control Hosp Epidemiol. 2010;31(4):341-7.

52. Carbonne A, Thiolet JM, Fournier S, Fortineau N, Kassis-Chikhani N, Boytchev I, et al. Control of a multi-hospital outbreak of KPC-producing Klebsiella pneumoniae type 2 in France, September to October 2009. Euro Surveill. 2010;15(48).

53. Steinmann J, Kaase M, Gatermann S, Popp W, Steinmann E, Damman M, et al. Outbreak due to a Klebsiella pneumoniae strain harbouring KPC-2 and VIM-1 in a German university hospital, July 2010 to January 2011. Euro Surveill. 2011;16(33).

54. Robustillo Rodela A, Diaz-Agero Perez C, Sanchez Sagrado T, Ruiz-Garbajosa P, Pita Lopez MJ, Monge V. Emergence and outbreak of carbapenemase-producing KPC-3 klebsiella pneumoniae in Spain, September 2009 to February 2010: Control measures. Euro Surveill. 2012;17(7).

55. Munoz-Price LS, De La Cuesta C, Adams S, Wyckoff M, Cleary T, McCurdy SP, et al. Successful eradication of a monoclonal strain of Klebsiella pneumoniae during a K. pneumoniae carbapenemase-producing K. pneumoniae outbreak in a surgical intensive care unit in Miami, Florida. Infect Control Hosp Epidemiol. 2010;31(10):1074-7.

C. Excluded: unobtainable study (one study)

56. Shenoy S, Hegde A, Saldanha Dominic RM, Kamath S, Arvind N. An outbreak of extended spectrum beta-lactamase producing Klebsiella pneumoniae in a neonatal intensive care unit. Indian J Pathol Microbiol. 2007;50(3):669-70

Appendix 4. List of studies meeting the inclusion criteria for the review

A. Studies meeting the inclusion criteria and included in the review analyses (6 studies, 7 publications)

The following studies met the inclusion criteria and provided sufficient information to meet the ORION statement [4] for criteria 9 (intervention reporting) and 17 (outcome reporting and estimation). These studies were included in the analysis, and their data and findings form the basis of this report and its conclusions and recommendations.

Study ID*	Bibliographic details of publication(s)**
Borer 2011	Borer A, Eskira S, Nativ R, Saidel-Odes L, Riesenberg K, Livshiz-Riven I, et al. A multifaceted intervention strategy for eradication of a hospital-wide outbreak caused by carbapenem-resistant *Klebsiella pneumoniae* in southern Israel. Infect Control Hosp Epidemiol 2011;32 (12):1158-1165.
Chitnis 2012	Chitnis AS, Caruthers PS, Rao AK, Lamb J, Lurvey R, Beau De Rochars V, et al. Outbreak of carbapenem-resistant enterobacteriaceae at a long-term acute care hospital: sustained reductions in transmission through active surveillance and targeted interventions. Infection Control & Hospital Epidemiology 2012;33 (10):984-92.
Ciobotaro 2011	Ciobotaro P, Oved M, Nadir E, Bardenstein R, Zimhony O. An effective intervention to limit the spread of an epidemic carbapenem-resistant *Klebsiella pneumoniae* strain in an acute care setting: From theory to practice. Am J Infect Control 2011;39 (8):671-677.
Cohen 2011	Cohen MJ, Block C, Levin PD, Schwartz C, Gross I, Weiss Y, et al. Institutional control measures to curtail the epidemic spread of carbapenem-resistant *Klebsiella pneumoniae*: a 4-year perspective. Infection Control & Hospital Epidemiology 2011;32 (7):673-8.
Poulou 2012	Poulou A, Voulgari E, Vrioni G, Xidopoulos G, Pliagkos A, Chatzipantazi V, et al. Imported *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* clones in a Greek hospital: Impact of infection control measures for restraining their dissemination. J Clin Microbiol 2012;50 (8):2618-2623. Poulou A, Markou F, Voulgari E, Ranellou K, Vrioni G, Tsakris A. Effectiveness of infection control measures and active surveillance to reduce the prevalence of carbapenem-resistant Klebsiella pneumoniae in an acute care Greek hospital. In: Clinical Microbiology and Infection. Presented at 22nd European Congress of Clinical Microbiology and Infectious Diseases; 31 Mar - 3 Apr 2012; London: UK. Clinical Microbiology and Infection. 2012;18.
Schwaber 2014	Schwaber MJ, Lev B, Israeli A, Solter E, Smollan G, Rubinovitch B, Shalit I, Carmeli Y. Containment of a country-wide outbreak of carbapenem-resistant *Klebsiella pneumoniae* in israeli hospitals via a nationally implemented intervention. Clin Infect Dis 2011;52 (7):848-855. Schwaber MJ, Carmeli Y. An ongoing national intervention to contain the spread of carbapenem-resistant enterobacteriaceae [Internet] *Clin Infect Dis*. 2014 Jan 6. 2014 [Accessed 5.2.14]. Available from: http://cid.oxfordjournals.org/content/early/2014/01/05/cid.cit795.full.pdf+html

** Study ID used throughout the review*

*** Main publication shown first; additional publications or duplicate publications of the same data are shown in italics. Data extraction is based on the main publication. Other relevant information was extracted as required from additional publications.*

B. Studies meeting the inclusion criteria but not included in the review analyses (44 studies, 48 publications)

The following studies met the inclusion criteria and but *did not* provide sufficient information to meet ORION statement [4] for criteria 9 (intervention reporting) and 17 (outcome reporting and estimation) or in the case of one study, was previously included in the original 2011 ECDC risk assessment (Munoz-Price 2010). These studies have been summarised below but *have not been* included in the analysis, as there was insufficient data and information to analyse in a meaningful way.

Study ID*	Bibliographic details of publication(s)**
Agodi 2011	Agodi A, Voulgari E, Barchitta M, Politi L, Koumaki V, Spanakis N, Giaquinta L, Valenti G, Romeo MA, Tsakris A. Containment of an outbreak of KPC-3-producing *Klebsiella pneumoniae* in Italy. J Clin Microbiol 2011;49 (11):3986-9.

Study ID*	Bibliographic details of publication(s)**
Ahmed-Bentley 2013	Ahmed-Bentley J, Chandran AU, Joffe AM, French D, Peirano G, Pitout JDD. Gram-negative bacteria that produce carbapenemases causing death attributed to recent foreign hospitalization. Antimicrob Agents Chemother 2013;57 (7):3085-3091. Chandran AU, Wolfe A-L, Manca S, Ahmed-Bentley J, Pitout J, Barclay J, Joffe AM. Investigation of a multiple multidrug-resistant gram-negative bacilli outbreak in a Canadian hospital (OR 'Help!!! We Have CRE!!!'). Poster presented at ID Week; 17-21 Oct 2012; San Diego: CA. 2012.
Apisarnthanarak 2012	Apisarnthanarak A, Kiratisin P, Khawcharoenporn T, Warren DK. Using an intensified infection prevention intervention to control carbapenemase- producing Enterobacteriaceae at a Thai center. Infect Control Hosp Epidemiol 2012;33 (9):960-961.
Balkhy 2012	Balkhy HH, El-Saed A, Al Johani SM, Francis C, Al-Qahtani AA, Al-Ahdal MN, Altayeb HT, Arabi Y, Alothman A, Sallah M. The epidemiology of the first described carbapenem-resistant *Klebsiella pneumoniae* outbreak in a tertiary care hospital in Saudi Arabia: How far do we go? Eur J Clin Microbiol Infect Dis 2012;31 (8):1901-1909. Balkhy HH, El-Saed A, Al Johani S, Tayeb HT, Al-Qahtani A, Alahdal M, Sallah M, Alothman A, Alarabi Y. Epidemiology of the first outbreak of carbapenem-resistant *Klebsiella pneumoniae* in Saudi Arabia. In: BMC Proceedings. Conference: International Conference on Prevention and Infection Control, ICPIC 2011 Geneva Switzerland. Conference Start: 20110629 Conference End: 20110702. Conference Publication: (var.pagings). 5 , 2011. Date of Publication: 29 Jun 2011., 2011
Ben-David 2010	Ben-David D, Maor Y, Keller N, Regev-Yochay G, Tal I, Shachar D, Zlotkin A, Smollan G, Rahav G. Potential role of active surveillance in the control of a hospital-wide outbreak of carbapenem-resistant *Klebsiella pneumoniae* infection. Infection Control & Hospital Epidemiology 2010;31 (6):620-6
Bernaschi 2013	Bernaschi P, Del Chierico F, Petrucca A, Argentieri A, Ciofi Degli Atti M, Ciliento G, Carletti M, Muraca M, Locatelli F, Putignani L. Microbial tracking of multidrug-resistant *Klebsiella pneumoniae* isolates in a pediatric hospital setting. International Journal of Immunopathology & Pharmacology 2013;26 (2):463-72.
Borgia 2012	Borgia S, Lastovetska O, Richardson D, Eshaghi A, Xiong J, Chung C, Baqi M, McGeer A, Ricci G, Sawicki R, Pantelidis R, Low DE, Patel SN, Melano RG. Outbreak of carbapenem-resistant enterobacteriaceae containing bla NDM-1, Ontario, Canada. Clin Infect Dis 2012;55 (11):e109-e117.
Carbonne 2010	Carbonne A, Thiolet JM, Fournier S, Fortineau N, Kassis-Chikhani N, Boytchev I, Aggoune M, Seguier JC, Senechal H, Tavolacci MP, Coignard B, Astagneau P, Jarlier V. Control of a multi-hospital outbreak of KPC-producing *Klebsiella pneumoniae* type 2 in France, September to October 2009. Eurosurveillance 2010;15 (48).
Carrilho 2011	Carrilho C, Pascual Garcia JC, Belei RA, Paiva NS, Cornetta NJ, Oricolli RL, Grion C, Pelisson M, Costa SF. Outbreak of carbapenem-resistant enterobacteria in a Brazilian university hospital. In: Clinical Microbiology and Infection. Conference: 21st ECCMID/27th ICC Milan Italy. Conference Start: 20110507 Conference End: 20110510. Conference Publication: (var.pagings). 17 (pp S775-S776), 2011.
CDC MMWR 2012	Centers for Disease C, Prevention. Carbapenem-resistant Enterobacteriaceae containing New Delhi metallo-beta-lactamase in two patients - Rhode Island, March 2012. MMWR Morb Mortal Wkly Rep 2012;61 (24):446-8.
Dautzanberg 2012	Dautzenberg MJD, Ossewaarde JM, Van Der Zee A, De Kraker MEA, De Greeff SC, Grundmann H, Bijlmer HA, Troelstra A, Bonten MJM. Successful control of a large outbreak of OXA-48 producing Enterobacteriaceae in the Netherlands. In: Clinical Microbiology and Infection. Presented at 22nd European Congress of Clinical Microbiology and Infectious Diseases; 31 Mar - 3 Apr 2012; London: UK. Clinical Microbiology and Infection. 2012;18.
Diederen 2011	Diederen B, Hattink C, De Groot M. Transmission of KPC-producing *Klebsiella pneumoniae* despite appropriate barrier precautions of an intensive care unit in the Netherlands. In: BMC Proceedings. Conference: International Conference on Prevention and Infection Control, ICPIC 2011 Geneva Switzerland. Conference Start: 20110629 Conference End: 20110702. Conference Publication: (var.pagings). 5 , 2011. Date of Publication: 29 Jun 2011., 2011.
Espasa-Soley 2012	Espasa-Soley M, Fernandez I, Oteo J, Sanchez-Fresquet X, Falgueras L, Vindel A, Capilla S, Piriz M, Saez D, Sanfeliu I, Navarro G, Campos J, Fontanals D, Segura F. A nosocomial outbreak of a carbapenem-resistant *Klebsiella pneumoniae* ST-663 producing OXA-48 and CTX-M-15 related to a duodenoscope contamination. In: Clinical Microbiology and Infection. Presented at 22nd European Congress of Clinical Microbiology and Infectious Diseases; 31 Mar - 3 Apr 2012; London: UK. Clinical Microbiology and Infection. 2012;18.
Fankhauser 2011	Fankhauser C, Cherkaoui A, Renzi G, Abbas M, Schrenzel J, Pittet D, Harbarth S. Carbapenem-resistant enterobacteriacae: A challenge for early detection and infection control. In: BMC Proceedings. Conference: International Conference on Prevention and Infection Control, ICPIC 2011 Geneva Switzerland. Conference Start: 20110629 Conference End: 20110702. Conference Publication: (var.pagings). 5 , 2011. Date of Publication: 29 Jun 2011., 2011. Fankhauser C, Cherkaoui A, Renzi G, Schrenzel J, Harbarth S. First documented New Delhi metallo-beta-lactamase 1 (NDM-1) cases in Switzerland. In: Clinical Microbiology and Infection. Conference: 21st ECCMID/27th ICC Milan Italy. Conference Start: 20110507 Conference End: 20110510. Conference Publication: (var.pagings). 17 (pp S139), 2011. Date of Publication: May 2011., 2011.

Study ID*	Bibliographic details of publication(s)**
Fournier 2012	Fournier S, Brun-Buisson C, Jarlier V. Twenty years of antimicrobial resistance control programme in a regional multi hospital institution, with focus on emerging bacteria (VRE and CPE). Antimicrob 2012;1 (1):9.
Gopalakrishnan 2010	Gopalakrishnan R, Sureshkumar D. Changing trends in antimicrobial susceptibility and hospital acquired infections over an 8 year period in a tertiary care hospital in relation to introduction of an infection control programme. The Journal of the Association of Physicians of India 2010;58 Suppl:25-31.
Greene 2011	Greene LR. Investigation of a cluster of *Klebsiella pneumoniae* Carbapenemase-producing organisms on a long-term care ventilator unit. In: American Journal of Infection Control. Conference: 38th Annual Educational Conference and International Meeting of the Association for Professionals in Infection Control and Epidemiology, Inc., APIC 2011 Baltimore, MD United States. Conference Start: 20110627 Conference End: 20110629. Conference Publication: (var.pagings). 39 (5) (pp E118).
Gregory 2010	Gregory CJ, Llata E, Stine N, Gould C, Santiago LM, Vazquez GJ, Robledo IE, Srinivasan A, Goering RV, Tomashek KM. Outbreak of carbapenem-resistant *Klebsiella pneumoniae* in Puerto Rico associated with a novel carbapenemase variant. Infect Control Hosp Epidemiol 2010;31 (5):476-484.
Ingold 2012	Ingold A, Echeverria N, Acevedo A, Borthagaray G, Vignoli R, Viroga J, Gonzalez O, Odizzio V, Etulain K, Nunez E, Marquez C, Albornoz H, Galiana A. KPC-producing *Klebsiella pneumoniae* in Uruguay: First two clinical cases and isolates' characteristics report. In: Clinical Microbiology and Infection. Presented at 22nd European Congress of Clinical Microbiology and Infectious Diseases; 31 Mar - 3 Apr 2012; London: UK. Clinical Microbiology and Infection. 2012;18.
Kaase 2012	Kaase M, Eckmanns T, Pfennigwerth N, Szabados F, Gatermann S. Carbapenemases found in patients from libyia. In: International Journal of Medical Microbiology. Conference: 64. Jahrestagung der Deutschen Gesellschaft fur Hygiene und Mikrobiologie, DGHM Hamburg Germany. Conference Start: 20120930 Conference End: 20121003. Conference Publication: (var.pagings). 302 (pp 91), 2012. Date of Publication: September 2012., 2012.
Karampatakis 2012	Karampatakis T, Athanasoula E, Sianou E, Pistofidis K, Aretaki E, Repana I, Sevastidou A, Orfanou A, Siaka E. Outbreak of carbapenemase-producing *Klebsiella pneumoniae* and Enterobacter cloacae strains in a Greek University Hospital. In: Clinical Microbiology and Infection. Presented at 22nd European Congress of Clinical Microbiology and Infectious Diseases; 31 Mar - 3 Apr 2012; London: UK. Clinical Microbiology and Infection. 2012;18.
Kassis-Chikhani 2010	Kassis-Chikhani N, Saliba F, Carbonne A, Neuville S, Decre D, Sengelin C, Guerin C, Gastiaburu N, Lavigne-Kriaa A, Boutelier C, Arlet G, Samuel D, Castaing D, Dussaix E, Jarlier V. Extended measures for controlling an outbreak of VIM-1 producing imipenem-resistant *Klebsiella pneumoniae* in a liver transplant centre in France, 2003-2004. Euro surveillance: bulletin europeen sur les maladies transmissibles = European communicable disease bulletin 2010;15 (46). Kassis-Chikhani N, Saliba F, Carbonne A, Neuville S, Decre D, Sengelin C, et al. Extented measures for controlling an outbreak of VIM-1 producing imipenem-resistant *Klebsiella pneumoniae* in a liver transplant centre in France, 2003-2004. Eurosurveillance 2010;15 (46).
Kotsanas 2013	Kotsanas D, Wijesooriya WRPLI, Korman TM, Gillespie EE, Wright L, Snook K, Williams N, Bell JM, Li HY, Stuart RL. "Down the drain": carbapenem-resistant bacteria in intensive care unit patients and handwashing sinks. Med J Aust 2013;198 (5):267-9.
Lowe 2013	Lowe CF, Kus JV, Salt N, Callery S, Louie L, Khan MA, Vearncombe M, Simor AE. Nosocomial transmission of New Delhi metallo-b-lactamase-1- producing *Klebsiella pneumoniae* in Toronto, Canada. Infect Control Hosp Epidemiol 2013;34 (1):49-55.
Mammina2012	Mammina C, Bonura C, Di Bernardo F, Aleo A, Fasciana T, Sodano C, Saporito MA, Verde MS, Tetamo R, Palma DM. Ongoing spread of colistin-resistant *Klebsiella pneumoniae* in different wards of an acute general hospital, Italy, June to December 2011. 2012: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin. 17 (33), 2012.
Meessen 2010	Meessen N, Wiersinga J, Van Der Zwaluw K, Van Altena R. First outbreak of carbapenemase-producing *Klebsiella pneumoniae* in a tuberculosis care facility in the Netherlands. In: Clinical Microbiology and Infection. Conference: 20th ECCMID Vienna, Austria. 10 April–13 April 2010.
Monti 2012	Monti P, Folsi F, Bonfanti P, Pini B, Regazzoni F, Tentori C, Luzzaro F. Emergence of *Klebsiella pneumoniae* producing KPC-type enzymes and infection control measures for containing hospital spread. In: American Journal of Infection Control. Conference: 39th Annual Educational Conference and International Meeting of the Association for Professionals in Infection Control and Epidemiology, Inc., APIC 2012 San Antonio, TX United States. Conference Start: 20120604 Conference End: 20120606. Conference Publication: (var.pagings). 40 (5) (pp e87), 2012. Date of Publication: June 2012., 2012.
Morris 2012	Morris D, Boyle F, Morris C, Condon I, Delannoy-Vieillard AS, Power L, Khan A, Morris-Downes M, Finnegan C, Powell J, Monahan R, Burns K, O'Connell N, Boyle L, O'Gorman A, Humphreys H, Brisse S, Turton J, Woodford N, Cormican M. Inter-hospital outbreak of *Klebsiella pneumoniae* producing KPC-2 carbapenemase in Ireland. J Antimicrob Chemother 2012;67 (10):2367-2372.
Munoz-Price 2010	Munoz-Price LS, Hayden MK, Lolans K, Won S, Calvert K, Lin M, Stemer A, Weinstein RA. Successful control of an outbreak of *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* at a long-term acute care hospital. Infection Control & Hospital Epidemiology 2010;31 (4):341-7. (NOTE: Previously included in original ECDC 2011 technical report so not included as to avoid duplication of data)

Study ID*	Bibliographic details of publication(s)**
Otero 2012	Otero D, Pinheiro BP, Magalhaes ACG, Cardoso FLL, Affonso Mascarenhas L, Aranha Nouer S, Souza CRC, Mocali CG, Araujo EGP, Dias De Oliveira V, Afonso IF, Martins IS. Carbapenem-resistant Enterobacteriaceae surveillance: 2 years cohort with successful control. In: Clinical Microbiology and Infection. Presented at 22nd European Congress of Clinical Microbiology and Infectious Diseases; 31 Mar - 3 Apr 2012; London: UK. Clinical Microbiology and Infection. 2012;18.
Papadimitrou-Olivgeris 2012	Papadimitriou-Olivgeris M, Marangos M, Fligou F, Christofidou M, Bartzavali C, Anastassiou ED, Filos KS. Risk factors for KPC-producing *Klebsiella pneumoniae* enteric colonization upon ICU admission. J Antimicrob Chemother 2012;67 (12):2976-2981.
Park 2012	Park J, You J, Yang H. An nosocomial transmission of IMP-1 producing *K. pneumoniae* in a intensive care unit at a Korean hospital. In: Clinical Microbiology and Infection. Presented at 22nd European Congress of Clinical Microbiology and Infectious Diseases; 31 Mar - 3 Apr 2012; London: UK. Clinical Microbiology and Infection. 2012;18.
Reiner 2013	Reiner S, Callaghan M. Enhanced patient hand-hygiene in a stem cell transplant unit reduces multi-drug resistant organism prevalence. In: American Journal of Infection Control. Conference: 40th Annual Conference, APIC 2013 Ft Lauderdale, FL United States. Conference Start: 20130608 Conference End: 20130610. Conference Publication: (var.pagings). 41 (6 SUPPL. 1) (pp S106), 2013. Date of Publication: June 2013., 2013.
Robustillo Rodela 2012	Robustillo Rodela A, Diaz-Agero Perez C, Sanchez Sagrado T, Ruiz-Garbajosa P, Pita Lopez MJ, Monge V. Emergence and outbreak of carbapenemase-producing KPC-3 kKebsiella pneumoniae in Spain, September 2009 to February 2010: Control measures. Eurosurveillance 2012;17 (7).
Ronayne 2012	Ronayne A, O'Brien D, Wrenn C, Rose L, Roche C, Fitzgerald S, Fenelon L, Crowley B, Schaffer K. An outbreak of OXA-48 carbapenemase-producing *Klebsiella pneumoniae* in an Irish tertiary referral centre in 2011. In: Clinical Microbiology and Infection. Presented at 22nd European Congress of Clinical Microbiology and Infectious Diseases; 31 Mar - 3 Apr 2012; London: UK. Clinical Microbiology and Infection. 2012;18. Schaffer K, Ronayne A, O'Brien D, Wrenn C, Fitzgerald S, Fenelon L, Crowley B, Flynn A. An Outbreak of OXA-48 carbapenemase producing *Klebsiella pneumoniae* in an irish tertiary referral centre in 2011. In: International Journal of Medical Microbiology. Conference: 64. Jahrestagung der Deutschen Gesellschaft fur Hygiene und Mikrobiologie, DGHM Hamburg Germany. Conference Start: 20120930 Conference End: 20121003. Conference Publication: (var.pagings). 302 (pp 139), 2012. Date of Publication: September 2012., 2012.
Rosenberger 2011	Rosenberger LH, Hranjec T, Politano AD, Swenson BR, Metzger R, Bonatti H, Sawyer RG. Effective cohorting and "superisolation" in a single intensive care unit in response to an outbreak of diverse multi-drug-resistant organisms. Surgical Infections 2011;12 (5):345-350.
Rossi 2011	Rossi M, Migliorino G, Motta E, Foresti S, Bramati S, Malandrin S, Vanenti M, Lanfranco P, Vigano EF, Gori A. Evaluation of control measurement procedures in the prevention of carbapenemase-2 (KPC-2)-producing *Klebsiella pneumoniae* nosocomial transmission. In: Clinical Microbiology and Infection. Conference: 21st ECCMID/27th ICC Milan Italy. Conference Start: 20110507 Conference End: 20110510. Conference Publication: (var.pagings). 17 (pp S371), 2011. Date of Publication: May 2011., 2011.
Sprecher 2010	Sprecher H, Oren I, Finkelstein R, Tavleva I, Geffen Y. The changing epidemiology of carbapenem-resistant Enterobacteriaceae carriage in hospitalized patients. In: Clinical Microbiology and Infection. Conference: 20th ECCMID Vienna Austria. Conference Start: 20100410 Conference End: 20100413. Conference Publication: (var.pagings). 16 (pp S28), 2010. Date of Publication: April 2010., 2010. ILL status: VLP – Retrieved
Steinmann 2011	Steinmann J, Kaase M, Gatermann S, Popp W, Steinmann E, Damman M, Paul A, Saner F, Buer J, Rath PM. Outbreak due to a *Klebsiella pneumoniae* strain harbouring KPC-2 and VIM-1 in a German university hospital, July 2010 to January 2011. Eurosurveillance 2011;16 (33).
Themeli-Digalaki 2012	2015. Themeli-Digalaki K, Karageorgopoulos D, Zarkotou O, Kousouli E, Voulgari E, Koumaki V, Vrioni G, Chrysos G, Voutsinas D, Tsakris A. Effectiveness of a country-wide infection control programme targeting carbapenem-resistant Gramnegative pathogens: Experience from a tertiary care hospital in Greece. In: Clinical Microbiology and Infection. Presented at 22nd European Congress of Clinical Microbiology and Infectious Diseases; 31 Mar - 3 Apr 2012; London: UK. Clinical Microbiology and Infection. 2012;18.
Verma 2013	Verma A, Philpolthoward J, Baker A, Heaton N, Wade J, Dhawun A. Outbreak of bla VIM-4 carbapcnemase producing enterohacfcrinceac in a pediatric liver transplant centre: A new threat to our antibiotics armamentarium. In: Liver Transplantation. Conference: 19th Annual International Congress of the International Liver Transplantation Society, ILTS 2013 Sydney, NSW Australia. Conference Start: 20130612 Conference End: 20130615. Conference Publication: (var.pagings). 19 (6 SUPPL. 1) (pp S128), 2013. Date of Publication: June 2013., 2013.
Wendt 2010	Wendt C, Schutt S, Dalpke AH, Konrad M, Mieth M, Trierweiler-Hauke B, Weigand MA, Zimmermann S, Biehler K, Jonas D. First outbreak of *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* in Germany. Eur J Clin Microbiol Infect Dis 2010;29 (5):563-570.
Zagorlanou 2012	Zagorianou A, Sianou E, Iosifidis E, Dimou V, Protonotariou E, Miyakis S, Roilides E, Sofianou D. Microbiological and molecular characteristics of carbapenemase-producing *Klebsiella pneumoniae* endemic in a tertiary Greek hospital during 2004-2010. 2012:Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin. 17 (7), 2012.

Study ID*	Bibliographic details of publication(s)**
Zavascki 2012	Zavascki AP, Carvalhaes CG, da Silva GL, Tavares Soares SP, de Alcantara LR, Elias LS, Sandri AM, Gales AC. Outbreak of carbapenem-resistant Providencia stuartii in an intensive care unit. Infection Control & Hospital Epidemiology 2012;33 (6):627-30.

** Study ID used throughout the review*

*** The main publication is shown first, and additional publications or duplicate publications of the same data are shown in italics. Data extraction has been based on the main publication. In addition, any other relevant information has been extracted as required from the additional publications.*