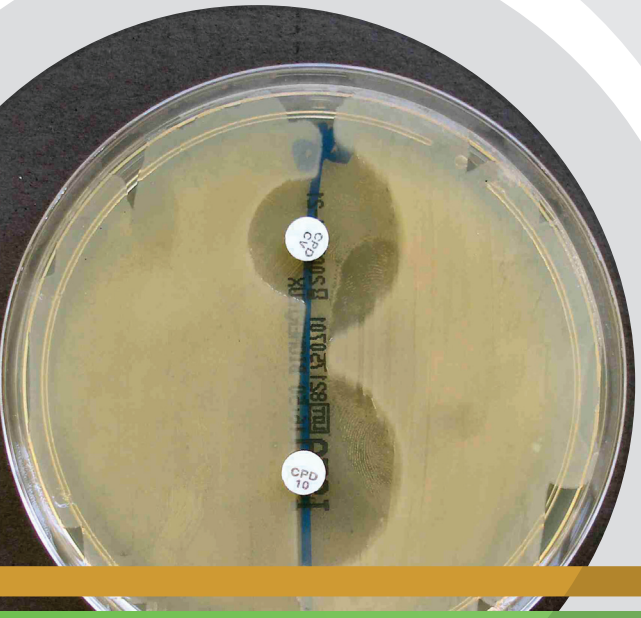

TECHNICAL REPORT

Systematic review of the effectiveness of infection control measures to prevent the transmission of extended-spectrum beta-lactamase-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 extended-spectrum beta-lactamase-producing Enterobacteriaceae through cross-border transfer of patients

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All above experts signed a declaration of interest prior to the meeting.

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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
ESBL-EC	Extended-spectrum β-lactamase-producing *Escherichia coli*
ESBL-KP	Extended-spectrum β-lactamase-producing *Klebsiella pneumoniae*
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
HDU	High-dependency unit (step-down, progressive, and intermediate care units)
HRE	Highly-resistant Enterobacteriaceae
HTA	Health Technology Assessment
ICU	Intensive care unit
KPC	*Klebsiella pneumoniae* carbapenemase
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-hydrolysing 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

Enterobacteriaceae that produce extended-spectrum β-lactamases (ESBL-E) carry plasmid-encoded enzymes that can efficiently hydrolyse and confer resistance to a variety of β-lactam antibiotics, but not to carbapenems or cephamycins. These enzymes are predominantly found in *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae* (*K. pneumoniae*), although present also in other members of the Enterobacteriaceae.

The emergence and spread of ESBL-E is a public health threat, especially because infections caused by ESBL-E are associated with an increase of morbidity, mortality, and healthcare costs. Curbing the spread of ESBL-E in healthcare facilities after their importation is important – as is controlling transmission in areas where they have become endemic – because they are associated with poor patient outcomes. Identifying the infection control measures that are effective 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 ESBL-E by creating new or modified guidelines/strategies for other MDROs, or national/local task forces, few official guidelines or guidance documents relating to infection control measures for ESBL-E have been published.

1.2 Aims and objectives

This systematic review sought to identify evidence for the effectiveness of targeted infection control measures to control the spread and transmission of ESBL-E when transferring patients between healthcare settings, especially when the transfer is cross-border. This evidence will be used by ECDC to develop guidance on this topic, to be used by countries in the European Union and the European Economic Area (EU/EEA) to help curb the transmission of ESBL-E into healthcare settings.

1.3 Methods

All stages of the review process adhered to published systematic review methods as recommended in the Cochrane Handbook and Centre for Reviews and Dissemination's (CRD) guidance for carrying out systematic reviews.

All studies, regardless of design, were selected for inclusion if they evaluated an infection control intervention for patients admitted or transferred to healthcare facilities who were at risk of becoming colonised or infected with ESBL-E. Relevant outcomes were the transmission or spread of ESBL-E within a healthcare facility. Items 9 and 17 from the 'Outbreak reports and intervention studies of nosocomial infection' (ORION) statement [1] were used as a criterion for the 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), the International Network of Agencies for Health Technology Assessment (INAHTA) database, 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 developed by 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.

Due to the heterogeneous nature of the studies, data were pooled, using appropriate meta-analyses, and a narrative synthesis of the studies was produced.

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 (GRADE; available from http://www.gradeworkinggroup.org/index.htm), with evidence from observational studies graded as '++'.

1.4 Results

A limited number of studies (10 out of 97) were included, two controlled and eight before-and-after studies. Three studies reported single-facet interventions, and the remaining seven listed interventions only as a part of multi-faceted bundles of infection control measures.

Half (n=5) were from Europe (France, Italy and Belgium), and the remaining five came from Australia, South Korea, the USA, Canada, and China. Five were from endemic areas, one was from a non-endemic area and no

information was provided for three studies. All studies were in acute-care healthcare settings, nine involving adult and one, paediatric populations. Three studies were conducted during an ESBL-E outbreak.

No studies specifically assessed the spread or transmission of ESBL-E during cross-border transfer, although two studies did report results for the numbers of cases imported from other units or hospitals within the same country.

The overall quality of the 10 studies included in the analysis was at best moderate. In general, the effectiveness of individual infection control measures was difficult to interpret because of various factors, including the following: the measures were implemented in multi-faceted bundles, compliance was poorly reported, there was a lack of controlled studies, and the reporting and quality of included studies was heterogeneous.

The low-grade evidence from the small number of included studies supports the effectiveness of following infection control measures for the prevention of spread of ESBL-E: antibiotic restriction, hand hygiene, contact precautions (gloves and gowns), active surveillance (screening) during an outbreak, patient cohorting, patient isolation, active screening on admission to a specific ward/unit, pre-emptive isolation of high-risk patients on admission, case notification/patient record flagging, bathing with antiseptic agents, nurse (or staff) cohorting (equivalent to dedicated nursing), dedicated staff and environmental cleaning (including post-patient discharge). These findings should be interpreted with caution and are at best suggestive of a possible effectiveness.

1.5 Discussion

This systematic review sought to provide an up-to-date summary of the best available evidence for interventions to control the transmission and spread of ESBL-E 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, poor reporting, the lack of single-intervention studies, variable compliance reporting, and the heterogeneity of 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

In this review, the following statements regarding the evidence for the effectiveness of infection control measures in reducing rates of ESBL-E colonisation and/or infection, can be made:

- No evidence was identified for infection control measures that were specifically implemented for the prevention of transmission of ESBL-E through cross-border transfer. Two studies, however, did report on the effectiveness of infection control measures implemented for imported cases of ESBL-E, including cases transferred within the same hospital. There is evidence that infection control measures are effective in reducing the spread of ESBL-E from cases imported into healthcare settings (evidence level ++).
- There is evidence, including evidence from single facet studies, for the effectiveness of antibiotic formulary changes and antibiotic restriction policies (evidence level ++).
- There is evidence from studies that report multi-faceted infection control bundles for the effectiveness of early implementation of: a) active surveillance (screening) by rectal screening for ESBL-E carriage on admission to specific wards/units, b) pre-emptive isolation of high-risk patients upon admission and c) active surveillance during outbreaks (evidence level ++).
- There is evidence from studies that report multi-faceted infection control bundles that the following infection control measures are effective: a) hand hygiene, b) contact precautions (gloves and gowns), c) patient cohorting, d) patient isolation, e) case notification/patient record flagging, f) bathing with antiseptic agents, g) nurse (or staff) cohorting (equivalent to dedicated nursing), h) antibiotic restriction policies, and i) reinforced environmental cleaning post patient discharge (evidence level ++).
- In these reviews, the best available evidence for the effectiveness of infection control interventions 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 ESBL-E.

2 Background

The transmission and spread of infectious diseases through population mobility, including multidrug-resistant organisms (MDROs) such as Enterobacteriaceae that produce extended-spectrum-beta lactamases (ESBL-E), is an increasing phenomenon. Cross-border transfer has been facilitated by the rise in the number of people who travel across borders for recreational and medical tourism, the repatriation of war casualties, and the transfer of patients between healthcare facilities [2-5].

Extended-spectrum beta-lactamases (ESBLs) are plasmid-encoded enzymes, predominantly found in *E. coli* and *Klebsiella pneumoniae* (*K. pneumoniae*), although present also in other members of the Enterobacteriaceae. ESBLs can hydrolyse and confer resistance to a variety of β-lactam antibiotics, including 2nd-, 3rd- and 4th-generation cephalosporins (e.g. ceftazidime, cefotaxime, ceftriaxone, and cefepime), monobactams (e.g. aztreonam) and penicillins (e.g. ampicillin, except temocillin). However, they do not confer resistance to carbapenems or cephamycins. ESBL-E can be transferred into healthcare settings via patients, causing healthcare-associated infections and outbreaks.

2.1 Classification

The most commonly used classification for β-lactamases is the one defined by Ambler, although the one by Bush-Jacoby-Medeiros is also used. The Ambler classification separates β-lactamases into four classes (Classes A–D) based on their molecular structure [6,7]. The Bush-Jacoby-Medeiros classification scheme separates β-lactamases by their function [7].

Class A β-lactamases have a serine at their active site [7,8] and are closely related to each other. The SHV, TEM, and CTX-M ESBL variants are Class A β-lactamases that are defined further as the functional group 2be, using the Bush-Jacoby-Medeiros scheme. In this functional group, the ESBL hydrolyses penicillins, oxyimino-cephalosporins and monobactams, but are inhibited by clavulanic acid, a β-lactamase inhibitor [7].

2.2 Epidemiology and worldwide spread

The emergence of extended-spectrum β-lactamases in Enterobacteriaceae in the 1980s was seen as a consequence of the introduction of third-generation cephalosporins which were widely used to treat infections with bacteria that produced TEM-1 and SHV-1 β-lactamases [9]. The first published report of plasmid-encoded β-lactamases that hydrolysed extended-spectrum cephalosporins was published in 1983 [10]. Since then, various ESBL types have been identified, including SHV, TEM, OXA, CTX-M, PER and VEB [11-14].

Risk factors for colonisation or infection with ESBL-E include prior stay in healthcare settings, foreign travel [15-17], prior antibiotic use, immunosuppression, and exposure to food and food-producing animals [18,19]. Colonisation and/or infection with ESBL-E can, therefore, occur not only in those patients who are debilitated, immunocompromised or critically ill, but also in otherwise healthy individuals.

Identifying potential carriers of ESBL-E upon admittance to a healthcare facility is important in order to implement effective control measures to prevent spread.

Even though rectal carriage of ESBL-E after hospital discharge has been well documented, the exact duration of carriage after discharge is not known. Studies point to a prolonged carriage of at least 12 months or longer [20,21], creating the potential for transmission of the ESBL-E to others in the community, including household contacts [21].

A number of reports have shown an increase in the prevalence of infections and/or rectal colonisation of people with ESBL-E, notably with the spread of the pandemic ST131 *E. coli* clone carrying the blaCTX-M-15 gene [22]. This increased prevalence of ESBL-E has been shown in travellers returning from abroad [15-17], the community [23-27], and patients admitted to healthcare facilities [28]. The spread of ESBL-E, like other highly-resistant gram-negative bacteria, is worrisome for public health because they are resistant to multiple antimicrobials, transmissible within healthcare systems, and can lead to colonisation and/or infection of patients, and can cause outbreaks when transferred into a new healthcare setting [3]. ESBL-E are frequently multidrug-resistant, exhibiting resistance to other antimicrobial classes such as fluoroquinolones, aminoglycosides and, trimethoprim-sulfamethoxazole due to associated resistance mechanisms, which may be either chromosomally or plasmid-encoded [14,22]. Furthermore, infections from ESBL-E are associated with poorer patient outcomes, increased morbidity, mortality, and higher hospital costs [29].

2.3 Issues in laboratory detection

Within the β-lactamase family, ESBLs comprise the largest and most prevalent group of enzymes [30]. Detecting ESBLs can be particularly challenging for a number of reasons, ranging from clinical and infection control to laboratory issues. Clinical or infection control issues can include lack of hospital or national infection control protocols that recommend active screening; incomplete evaluation of which patients should be actively screened or cultured, and resource-poor settings where implementation of infection control measures is difficult once presence of ESBL 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 are able to detect ESBL 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 ESBLs in Enterobacteriaceae [31-34].

While commercial media such as BKSE agar (AES Chemunex, France) and EbSA ESBL agar (AlphaOmega BV, the Netherlands) permit rapid detection of ESBL-E in screening samples, identifying the phenotype and organism is more problematic [30]. Tests such as combination disk, double-disk synergy and Etest presume that ESBL-E will have enhanced susceptibility in the presence of clavulanate, a β-lactamase inhibitor. Automated tests such as Vitek 2 (bioMérieux, France) and Phoenix (BD Diagnostics, USA) allow detection of ESBL and pure culture confirmation. Chromogenic media such as chromID ESBL (bioMérieux), Brilliance ESBL (Oxoid Ltd., United Kingdom), and CHROMagar ESBL (CHROMagar, France) combine ESBL detection with identification of the bacterium.

The type of antibiotics used to detect ESBL activity depends on the ESBL variant: cefpodoxime is a reliable substrate for most TEM and SHV ESBLs whereas a combination of ceftazidime and cefotaxime is required to detect CTX-M and some TEM ESBLs. However, a high production level of AmpC and K1 penicillinases can result in false positives due to porin or AmpC overexpression, rather than ESBL production [35]. For both screening and clinical samples, a drastic reduction in specificity can occur when evaluating strains with a high level of production of AmpC β-lactamases [30].

In the future, sequencing data and polymerase chain reaction (PCR)-microarray-based assays may meet the requirement for a rapid detection of ESBLs in patients at time of admission to hospital [30,36].

2.4 Issues in infection control

The spread of ESBL-E within hospitals has been shown to lead to hospital outbreaks especially where there are breaches in infection control. The emergence and spread of ESBL-E is a public health threat since infections with these MDROs are associated with worse outcomes, prolonged hospitalisation and higher mortality rates [37-39]. Carbapenems are the antibiotics of choice for treating infections with ESBL-E. The increased use of carbapenems, however, has led to a vicious cycle of antibiotic use and resistance, with the emergence of other MDROs such as carbapenemase-producing Enterobacteriaceae (CPE).

Knowing which infection control measures are effective and which should be implemented is of paramount importance. Because of the difficulties in assessing the effectiveness of these measures, the ORION statement [1] was developed as a standard for the transparent reporting of infection control interventions during outbreaks.

Guidelines and/or strategies that contain infection control recommendations referring only to ESBL-E are not available, but are embedded in guidelines for infection control for other MDROs [40,41]; guidelines have been published by the Health Protection Surveillance Centre, Ireland [42], and the Haut Conseil de la Santé Publique (HCSP), France [43]. Since guidelines are not available in each country, these documents are only examples and do not represent an exhaustive list.

3 Objectives

The objective was to carry out a systematic review of the evidence for the effectiveness of active screening and other targeted infection control measures when transferring patients between healthcare settings, especially across borders, who are carriers of ESBL-E. Given the likely lack of data regarding infection control measures specifically aimed at preventing the cross-border transfer of ESBL-E, interventions aimed at preventing and controlling the spread/transmission of ESBL-E between any type of healthcare facility, not necessarily involving cross-border transmission, were also included in the search.

The conclusions from this systematic review will be reviewed and used by an expert group coordinated by ECDC to develop guidance. This guidance will be available to Member States in the European Union and the European Economic Area (EU/EEA) to adapt or adopt in order to curb the spread of ESBL-E.

4 Methods

All stages of the review process (literature searching, study selection, study assessment, data analysis and report writing) involved rigorous attempts to reduce the risk of bias and error. This review adhered to published systematic review methods as recommended in the Cochrane Handbook [44] and the guidance on conducting systematic reviews published by the CRD [45]. All stages of the review process involved at least two reviewers working independently in order to check the validity and accuracy of both the review decisions and the report contents.

4.1 Inclusion criteria

This review is based on studies that were included because they met the following criteria:

4.1.1 Population

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

This included (but was not limited to) patients who were exposed to cases of ESBL-E introduced by cross-border transfer, or by introduction of ESBL-E to non-endemic or endemic healthcare facilities and countries.

'Healthcare facilities' included: 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.

4.1.2 Interventions and comparators

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

Screening: Performing active surveillance cultures, active screening tests, or contact screening of at-risk patients for the detection of colonisation with ESBL-E. Screening sites 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 ESBL-E, 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 ESBL-E, contact precautions for all patient care, ward closure, environmental cleaning and disinfection, antibiotic restriction or antibiotic class shift.

4.1.3 Outcome measures

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

Studies which did not report data on acquisition outcomes were excluded.

4.1.4 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 items 9 and 17 (intervention description and outcome assessment, respectively) of the ORION statement [1]. Details of the ORION statement are given in Table 1: Summary of reporting standards for transparent reporting of outbreak reports and intervention studies of nosocomial infection (ORION statement).

4.2 Literature searches

Search strategies were developed specifically for each database; 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 references, browsing database thesauri (e.g. MEDLINE MeSH and EMBASE Emtree), and initial scoping searches. These scoping searches and the existing ECDC review [2] 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.

The following databases were searched from inception to present (between 10 July 2013 and 17 July 2013):

- MEDLINE (OvidSP): 1946–2013/06/wk 4
- MEDLINE In-Process Citations and Daily Update (OvidSP): up to 9 July 2013
- EMBASE (OvidSP): 1974–2013/07/09
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): 2013/Issue 6
- Health Technology Assessment Database (HTA) (Wiley): 2013/Issue 2
- International Network of Agencies for Health Technology Assessment (INAHTA) Publication (internet): up to 13 July 2013, http://www.inahta.org/

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 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 or CRCT, 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. number of admissions or discharges, patient bed days). If possible, prevalence of organism and incidence of colonisation on admission at same time intervals. Criteria for infection, colonisation on admission and directly attributable mortality. For short studies or outbreak reports, use of charts with duration of patient stay and dates organism detected may be useful (see text).
Economic outcomes	12	If a 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, the dates of periods of recruitment and follow-ups need to be defined. A flow diagram is recommended to describe participant flow at each stage of the 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; it should be stated whether it was planned (specified in the protocol); possible confounders need to 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, an 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 the results be generalised for different target populations or settings and whether it is feasible to maintain an intervention in the long term.)
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

Full search strategies are reported in Appendix 1.

4.2.1 Reference checking

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

4.2.2 Handling of citations

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

4.2.3 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 [46,47].

4.3 Methods of study selection, quality assessment and data extraction

4.3.1 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. Disagreements were resolved through discussion and checked by a third reviewer. Justification for excluding studies was documented (see Appendix 3).

4.3.2 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) [1].

The methodological quality (risk of bias) of the trials was assessed independently by two reviewers using the criteria of Downs & Black (see Appendix 2 for further details) [48]. If studies were comparative (i.e. had two study arms each with a different intervention), the methodological quality of the studies was also assessed using the Cochrane Collaboration criteria (see Appendix 2 for further details) [49]. Disagreements were resolved by consensus and checked by a third reviewer. The results of the quality assessment were used for descriptive purposes to provide an evaluation of the overall quality of the included trials and to provide a transparent method of recommendation for the design of future studies.

4.3.3 Data collection

Data extraction sheets were individually designed and pilot-tested using Microsoft Excel 2007. For each study meeting the review inclusion criteria, the following general types of information/data were recorded: study ID, country/region, study aim, bacterial type, intervention details, study design, sample size and reported outcomes.

For those studies which also met the ORION statement for items 9 and 17 (intervention description and outcome assessment, respectively) [1] and which were to be included in the analysis section of the review, further details were extracted. These included population details, assessment methods, statistical analysis methods, study conclusions and actual outcome data. 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. Disagreements were resolved by checking the original paper and reaching consensus, otherwise a third reviewer was asked to resolve any outstanding discrepancy.

4.4 Data synthesis

Data synthesis centred on the studies which met the inclusion criteria, but also reported sufficient details of the intervention used (criterion 9) and the outcome data recorded (criterion 17) so that they met the ORION statement [1]. Studies which did not meet the required ORION criteria were summarised in tables, but not included in the review.

Data from the studies included in the analysis are grouped in the following categories:

- Studies of single-faceted interventions to prevent the transmission and spread of ESBL-E
- Studies of multi-faceted intervention to prevent the transmission and spread of ESBL-E.

A narrative summary of the studies included in the data synthesis was reported. This included a summary of the characteristics (e.g. study designs, population sizes, geographical location, year, baseline population characteristics, interventions, outcome definitions, etc.) and methodological quality of the studies. Risks which may introduce bias into the data or factors which may limit the generalisability of the findings were identified for the review findings as a whole as well as for the findings from individual studies. The data were summarised and where relevant, accompanied by 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 appropriate or possible.

The evidence to support each of the individual infection control measures was described using the Grading of Recommendations Assessment, Development and Evaluation Working Group (GRADE) evidence levels; available from http://www.gradeworkinggroup.org/index.htm), with evidence from observational studies graded as '++'.

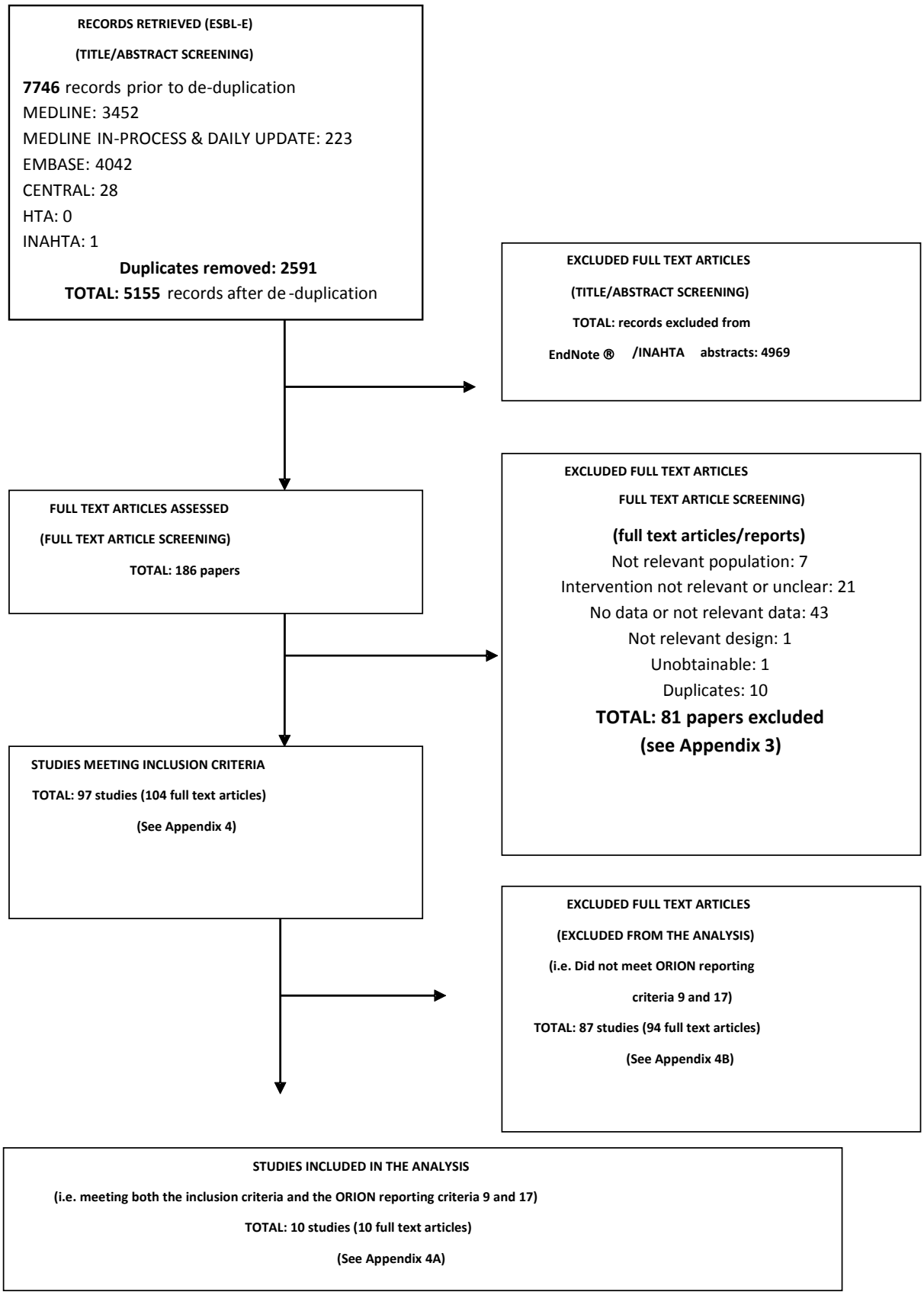
5 Results

5.1 Literature searches and inclusion assessment

In total, 5 155 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, 186 full text articles were ordered (185 were obtained) and screened in detail by two independent reviewers to determine whether they fulfilled the review inclusion criteria. A total of 81 full text articles were subsequently excluded for the following reasons: a) seven did not report a relevant population, b) in 21 full text articles the intervention was either irrelevant or unclear, c) in 43 full text articles there were no data or irrelevant results, and d) nine full text articles were duplicates. One full text article could not be accessed despite repeated efforts and therefore was classified as 'unobtainable'. Further details of the excluded trials are reported in Appendix 2.

In total, 97 separate studies reported in 104 publications met the inclusion criteria for the review (as described in Section 4.1). After further assessment to ensure that only the best available evidence was used to formulate the basis of this review and its conclusions, 10 studies (reported in 10 full text articles and listed in Appendix 4A) were selected for detailed analysis; the remaining 87 studies (reported in 94 full text articles and listed in Appendix 4B) are only briefly described.

Figure 1. Summary of study flow and selection



5.2 Overview of included studies

5.2.1 Study characteristics

Ninety-seven studies were judged to have met the inclusion criteria for the review. After further assessment using items 9 and 17 of the ORION statement [1], 10 studies were judged to provide sufficient detail and represent the best available evidence for the assessment of effectiveness. These studies are described below and form the basis of this review. The 87 studies (reported in 94 full text articles) which met the inclusion criteria, but which were not included in this analysis due to shortcomings in quality, are briefly described in Appendix 7.

The 10 studies used a mixture of study designs, including two controlled studies (Prospero 2010 [50] and Trick 2004 [51]) and eight studies which used a before-and-after design (Barbut 2013 [52], Conterno 2007 [53], Johnson 2005 [54], Laurent 2008 [55], Lee 2007 [56], Lucet 1999 [57], Souweine 2000 [58], and Wen 2010 [59]). Four of the studies were considered to be ambidirectional, in that they prospectively followed the effects of the intervention, but retrospectively identified pre-intervention infection levels (Barbut 2013 [52], Laurent 2008 [55], Lee 2007 [56], Lucet 1999 [57]). Four studies appeared to gather data only prospectively (Prospero 2010 [50], Trick 2004 [51], Wen 2010 [59], Conterno 2007 [53]), and two were retrospective studies (Johnson 2005 [54] and Souweine 2000 [58]).

The total sample of patients at risk of infection was often not reported. Where reported, this ranged from 286 (Trick 2004 [51]) to 358 (Wen 2010 [59]) patients, with between 30 (Laurent 2008 [55]) and 228 (Lee 2007 [56]) infected patients identified. The majority of studies gathered these data during the period 2000 to 2009 (Laurent 2008 [55], Johnson 2005 [54], Barbut 2013 [52], Lee 2007 [56], Prospero 2010 [50], Wen 2010 [59], Conterno 2007 [53]), though three studies used data gathered from the 1990s, including Trick 2004 [51] (1998 to 1999), Souweine 2000 [58] (1994 to 1996), and Lucet 1999 [57] (1989 to 1996).

Half of the studies were based in Europe (Barbut 2013 [52], Laurent 2008 [55], Lucet 1999 [57], Prospero 2010 [50], Souweine 2000 [58]), including three studies from France (Barbut 2013 [52], Lucet 1999 [57], Souweine 2000 [58]), one from Italy (Prospero 2010 [50]) and one from Belgium (Laurent 2008 [55]). The remaining studies were based in Australia (Johnson 2005 [54]), South Korea (Lee 2007 [56]), the USA (Trick 2004 [51]), Canada (Conterno 2007 [53]) and China (Wen 2010 [59]). Across all studies, three were centred on an outbreak of ESBL-E (Laurent 2008 [55], Lucet 1999 [57], Prospero 2010 [50]).

All of the studies were set in acute care hospitals, four included participants across the whole hospital (Johnson 2005 [54], Trick 2004 [51], Conterno 2007 [53], Wen 2010 [59]), while the others focussed on one or more specific wards or units. These included a burn unit (Barbut 2013 [52]), ICU (Laurent 2008 [55], Prospero 2010 [50], Souweine 2000 [58]) and a paediatric unit (Lee 2007 [56]). One study reported results across the whole hospital but also focussed on three specific wards/units, the ICU/HDU, a rehabilitation centre, and a step-down unit (Lucet 1999 [57]).

In many cases, the studies contained little description of the study population, failing even to report basic details of the population's age, gender, ethnicity and morbidities. Only five studies gave such descriptive details (Prospero 2010 [50], Souweine 2000 [58], Lee 2007 [56], Trick 2004 [51], and Wen 2010 [59]). Of the studies that provided descriptive details, one was based in a paediatric population with a mean patient age of 6.63 (SD 5.92) years (Lee 2007 [56]) and four were in adult populations, with mean ages ranging from 57.0 (SD 17.8) years (Prospero 2010 [50]) to 66.3 (SD 16.1) years (Wen 2010 [59]). One additional study in adults provided no details of the age of the patients (Barbut 2013 [52]). The proportion of male patients, where reported, ranged from 43% (Trick 2004 [51]) to 64.6% (Prospero 2010 [50]). Only one study gave details of the ethnicity of the included patients (Trick 2004 [51]). This study reported that 60–64% of the study sample were of 'black' ethnic origin.

The included studies all aimed to evaluate the impact of infection control measures, but none of the studies specifically targeted the control of ESBL-E transmission across borders. Six studies specifically identified the control of ESBL-E as their objective (Lee 2007 [56], Prospero 2010 [50], Wen 2010 [59], Conterno 2007 [53], Laurent 2008 [55], Lucet 1999 [57]). Three studies stated that their objective was to control the spread of MRSA and although they did not specifically mention ESBL-E, they did report on the levels of ESBL-E (Barbut 2013 [52], Johnson 2005 [54], Trick 2004 [51]). A fourth study (Souweine 2000 [58]) examined effective infection control measures for MRSA, but also reported the control of ESBL-E as an objective.

Three studies assessed single infection control measures (Prospero 2010 [50], Lee 2007 [56] and Wen 2010 [59]); all other studies assessed bundles of infection control measures. Further details of the measures are given in Table 2.

With respect to the identification of specific ESBL-E, four studies assessed the spread and transmission of ESBL-KP alone (Laurent 2008 [55], Prospero 2010 [50], Souweine 2000 [58], and Wen 2010 [59]) while four studies assessed the spread of both ESBL-KP and ESBL-EC (Conterno 2007 [53], Johnson 2005 [54], Lee 2007 [56], Trick 2004 [51]). Two studies failed to report the specific bacterial type, describing them only as 'ESBL-producing bacteria' or 'any ESBL' (Barbut 2013 [52], Lucet 1999 [57]). Where reported, identified phenotypes included: *K. pneumoniae* (PFGE B1, CTX-M15/PFGE A, CTX-M15) (Laurent 2008 [55]), *E. coli* and *K. pneumoniae* (Amp-C, CTX-M) (Lee 2007 [56]), and *K. pneumoniae* (predominantly Types 1 and 3) (Trick 2004 [51]). The studies (Barbut 2013 [52], Johnson 2005 [54] and Souweine 2000

[58]) were designed to monitor the transmission of MRSA and/or multidrug-resistant *Enterobacter aerogenes* (MREA) but also reported relevant data on ESBL-E.

Methods used in the detection of ESBL-E were variably reported. Only three studies reported and identified breakpoints. Breakpoints were taken from Clinical and Laboratory Standards Institute (CLSI) documents M100-S17 (Prospero 2010 [50]), M100-S15 (Lee 2007 [56]) and M100-S14 (Conterno 2007 [53]).

Four studies failed to clearly report the laboratory methods used (Barbut 2013 [52], Johnson 2005 [54], Prospero 2010 [50], Trick 2004 [51]). Among the other studies, the most frequently used methods were double-disk synergy (Conterno 2007 [53], Laurent 2008 [55], Lee 2007 [56], Lucet 1999 [57], Souweine 2000 [58], Wen 2010 [59]), polymerase chain reaction (PCR) and DNA sequencing to identify the specific genotype involved (Prospero 2010 [50], Laurent 2008 [55], Lee 2007 [56]); one study used automated methods (Laurent 2008 [55]).

Additionally, the source of the ESBL-E infection was not always clearly identified. Equally unclear was whether the infection involved the transfer of patients across geographical borders. Where information was available, it appeared that the infections were connected to transfers within the country (i.e. region/area to region/area) (Johnson 2005 [54], Lucet 1999 [57], Prospero 2010 [50], Souweine 2000 [58], Trick 2004 [51], Wen 2010 [59]). Similarly, it was often difficult to identify the type of healthcare setting from which the initial infection source had come from. When the infection source was reported, it appeared to involve the transfer of patients from the community to hospital and spread within the hospital (Conterno 2007 [53], Lucet 1999 [57], Barbut 2013 [52], Johnson 2005 [54], Laurent 2008 [55], Souweine 2000 [58]) or between wards/units within the same hospital (Prospero 2010 [50]). However, only two studies reported results for effects of infection control measures on the number of imported cases before and after the intervention (Laurent 2008 [55], Lucet 1999 [57]).

Further details of individual studies are described in the following results section and can also be found in Appendix 5.

Table 2. Summary of infection control measures included in single and multi-faceted studies

Study reference (first author, year)	Single-/multi-faceted	Active screening on admission to hospital	Active screening on admission to	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 staff	Bathing with anti-septic agent	Contact pre-cautions	Hand hygiene	Ward closure	Hospital closure	Patient record flagging	Antibiotic restriction	Environmental cleaning post-discharge	Other interventions and other details of the 2-arm studies
Barbut 2013 [52]	MF	X			X			X	X	X	X	X		X	X	X	X	[a]	Other: none
Conterno 2007 [53]	MF	X	X	X	X		X		X	X	X			X	X		X		Other: dedicated patient equipment
Johnson 2005 [54]	MF	X	X	X	X	X	X	X	X	X				X	X		X	X	Other: OCS[1]; alcohol-impregnated wipes for shared equipment
Laurent 2008 [55]	MF	X			X						X			X	X	X	X	[b]	Other: optimisation of bed occupancy
Lee 2007 [56]	S	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	Other: none
Lucet 1999 [57]	MF	X			X				X	X	X			X	X		X	X	Other: SDD[2] for the first year
Prospero 2010 [50] (Two-armed study)	S	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	Arm 1: used alcohol hand rub
	S	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	Arm 2: no alcohol hand rub
Souweine 2000 [58]	MF	X			X		X		X	X				X	X	X	X	X	Other: in-ward education for implementation of ICM[3]
Trick 2004 [51] (Two-armed study)	MF	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	Arm 1: contact isolation
	MF	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	Arm 2: routine glove use
Wen 2010 [59]	S	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	Other: none

✓: Component is included; X: component is not included

[a] Hydrogen peroxide vapour disinfection of room post-patient discharge; [b] reinforced cleaning of rooms post discharge; [1] OCS: Operation Clean Start [60]; [2] SDD: selective digestive decontamination; [3] ICM: infection control measures

5.2.2 Methodological quality of the studies

The overall quality of the ten studies included in the analysis was at best moderate (see Table 3 and 4). All studies had methodological issues which may introduce a risk of bias, and most studies were of poor to moderate quality. However, all the studies adequately described their aims (Downs & Black, criterion 1), interventions (Downs & Black, criterion 2), and outcomes (Downs & Black, criterion 4), and were carried out in representative populations (Downs & Black, criterion 20) and settings (Downs & Black, criterion 13). Despite this, elements of bias were present in all studies, not only because observational studies have an inherent risk of bias, but also because certain criteria in the Downs & Black checklist (see Tables 3 and 4) were not met. The presence of bias affects the validity and reliability of the findings.

In terms of hierarchy of evidence, the two controlled studies (Prospero 2010 [50] and Trick 2004 [51]) represent a higher level of evidence when compared to the remaining eight studies which use a before-and-after design. However, when considered individually and against criteria for the assessment of controlled studies (Cochrane Collaboration criteria [49], see Table 4), neither of the two controlled studies appeared to be of good quality, and both had methodological issues which may impact on their reliability. In particular it was difficult to assess the risk of bias within the study by Trick 2004 [51] due to poor and confusing reporting of the methods. The blinding of the intervention to patients and caregivers (which is an important consideration in all studies, including controlled trials) was not feasible given the area of research.

Given the nature of the before-and-after study design, such studies are subject to known risks of bias, including the risk of confounding through the inevitable selection of patients (pre-intervention and post-intervention) from different time periods (Downs & Black, criterion 22). This introduces the risk of confounding whereby factors other than those included in the intervention may have an influence on the observed effects on the spread of ESBL-E. This was acknowledged by some, but not all, authors when discussing the limitations of their study, and judging the influence of these potential confounders was difficult. None of the studies accounted for potential confounding when analysing their findings (Downs & Black, criterion 25). Ideally, a controlled study design with a single intervention control measure is used to make a proper assessment of the effectiveness of the infection control interventions. 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 ESBL-E infection and transmission.

Other main areas of concern across the included studies relate to lack of assessment of adverse events (Downs & Black, criterion 8) and the poor description of study populations (Downs & Black, criterion 3). Only half of the 10 studies (Lee 2007 [56], Prospero 2010 [50], Souweine 2000 [58], Trick 2004 [51] and Wen 2010 [59]) provided adequate basic information about the participants in the study. Only two studies (Laurent 2008 [55] and Lee 2007 [56]) mentioned the potential adverse effects of the intervention under evaluation. These are important factors to be considered before the implementation of any new intervention in order to make sure that new infection control measures are not going to be detrimental (or that effects are considered and, if possible, controlled), or applied to the wrong population/setting where their effects may not be as beneficial.

No other apparent risk of bias was evident or was reported for two studies (Barbut 2013 [52] and Prospero 2010 [50]). The remaining full text articles did not specifically report on risk of bias; however, issues were reported by the authors or were evident from the findings, which may also have influenced the risk of bias in these studies.

In the study by Conterno 2007 [53], contact precautions, as a pre-infection control measure, were used in only 28% of ESBL-E cases, potentially underestimating the effect of the infection control measure, and a general increase in antibiotic use was recorded throughout the study period. The authors also noted that it was difficult to determine how routine surveillance cultures would influence the nosocomial ESBL-E incidence rate (incidence may have been underestimated).

The use of computer databases to measure total clinical isolates of MRSA (or ESBL-Es) overestimates the true burden of nosocomial infections and may have affected the findings reported by Johnson 2005 [54]. The control of MRSA transmission was the main focus of this study (not ESBL-E) and information regarding the potential bias with respect to the effect on ESBL-E is limited. The study also relies on data from historical controls, which could mean that changes outside the actual infection control measures are responsible for the observed improvements (e.g. Hawthorne effect', which refers to a phenomenon whereby individuals improve or modify an aspect of their behaviour in response to their being observed.). Confounding is also possible through the use of a concurrent computerised infection control programme which was in operation and was increasingly used over the study period. Therefore, the influence of antibiotic control and other infection practices cannot be ruled out.

Similar issues with regard to the potential effects of background antibiotic levels also apply to the studies by Laurent 2008 [55] and Lee 2007 [56]. Lee 2007 [56] assessed a change in antibiotic policy: only parenteral antibiotic use was included in the analysis, but oral antibiotics could have influenced the prevalence of ESBL-E. In addition, this study was too short to observe the true effects of infection control measure in ESBL-KP.

In the study by Lucet 1999 [57], routine screening was not performed in all units so that other paths of infection could not be ruled out. The percentage of ESBL-KP isolates decreased during the infection control measure period, which may have contributed to the successful control of single epidemic strains in the study.

A decrease in the mean ICU length of stay may have had an impact on the overall results of the study by Souweine 2000 [58]. The small sample size of this study may have made it impossible to detect a significant difference in the number of patients with infections or colonisations. A similar issue with small sample size was identified for Trick 2004 [51] although numbers were similar in both infection control measure groups. Trick 2004 used a controlled study design, and residents in one infection control measure arm (routine glove use) were significantly more likely to be culture-positive for ESBL-EC on their initial study swab than the other arm (contact isolation), which may have been a confounding factor. In the study by Wen 2010 [59], pre- and post-infection rates were very low and may not have been sufficient to detect a difference between the two study periods. The authors of this study also suggested a more cautious interpretation of the P-value for differences in acquisition rates, as the chi-squared test used is only valid only for independent observations. However, when considering infections with the same bacteria over the same time period and in the same department, this was not the case.

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

Study name	Downs & Black assessment criteria 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
Barbut 2013 [52]			■		■		■	■						X	X	X	X					■	X	X			
Conterno 2007 [53]			■		■		■	■						X	X	X	X		■			■	X	X	■		
Johnson 2005 [54]			■		■			■						X	X	X	X		■			■	X	X	■		
Laurent 2008 [55]			■		■									X	X	X	X					■	X	X	■		
Lee 2007 [56]					■									X	X	X	X					■	X	X			
Lucet 1999 [57]			■		■			■						X	X	X	X					■	X	X			
Prospero 2010 [50]								■		■				■	■	X	X				■		■	■			
Souweine 2000 [58]					■		■	■						X	X	X	X					■	X	X			
Trick 2004 [51]								■						■		X	X		■		■		■	■	X	■	
Wen 2010 [59]					■		■	■						X	X	X	X					■	X	X			

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

Note: Prospero 2010 [50] and Trick 2004 [51] are comparative (two-arm) studies and were also assessed using the Cochrane Collaboration quality assessment criteria.

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%?

Table 4. Summary of individual study quality for controlled studies using the Cochrane Collaboration assessment criteria

Study ID	Adequate randomi-sation	Adequate allocation conceal-ment	Participants blinded?	Assessors blinded?	Incomplete outcome data?	Selective reporting?	Other biases
Prospero 2010 [50]							
Trick 2004 [51]							

White = low risk of bias (i.e. high quality); black = high risk of bias (i.e. poor quality); grey = unclear risk of bias
See Appendix 2B for details of the actual criteria.

5.3 Single-faceted studies

Three of the included studies assessed single-facet infection control measures (Prospero 2010 [50], Lee 2007 [56] and Wen 2010 [59]).

One of these studies used a comparative, two-arm design (Prospero 2010 [50]) and the other two assessed the incidence/prevalence of ESBL-E before and after the infection control measure (Lee 2007 [56], Wen 2010 [59]). All of the studies assessed compliance with the infection control measures (Table 5).

Table 5. Summary of compliance assessment in single-faceted studies to control the spread of ESBL-E

Study ID	Compliance tested	Details (assessed facet and results of compliance assessment)
Lee 2007 [56]	Yes	*Changes to antibiotic formulary* Use of piperacillin/tazobactam in oncology ward increased from 4.5 to 155.6 AD, and use of extended-spectrum cephalosporins decreased from 170.5 to 26.9 AD, comparing pre- and post-intervention period (both p for trend 0.001). Use of piperacillin/tazobactam in paediatric wards increased from 1.4 to 89.2 AD, and use of extended-spectrum cephalosporin decreased from 176.4 to 124.6 AD (p for trend 0.001 and 0.002, respectively).
Prospero 2010 [50] (Two-armed study)	Yes	*Hand hygiene* Between 18 March and 30 September 2006, alcohol-based hand rub consumption in ICU A had been about 25 L/1000 pt days.
Wen 2010 [59]	Yes	*Changes to antibiotic formulary* 92.5% and 100% reduction in the use of third- and fourth-generation cephalosporins used in Phase IIb as compared with Phase I, respectively. Simultaneously, the use of second-generation cephalosporins more than doubled from Phase I to Phase IIb.

p = p-value; ICU = intensive care unit; L = litre; pt = patient; AD = admission days/year

Of the three studies on single infection control measures, two assessed a change in antibiotic policy unrelated to outbreaks (Lee 2007 [56], Wen 2010 [59]). Both studies were conducted in Asia, and the single infection control measure consisted of replacing cephalosporins with a piperacillin–tazobactam combination (Lee 2007 [56] and Wen 2010 [59]) or ampicillin–sulbactam combination (Lee 2007 [56]). The studies assessed compliance by reporting

antibiotic use during the study period, and they both reported large reductions in cephalosporin use and increases in piperacillin/tazobactam use.

In Lee 2007 [56], the antibiotic restrictions took place over three phases: 1) usual use of extended-spectrum cephalosporins for empirical or specific antibiotics; 2) piperacillin–tazobactam was encouraged for most patients (with the exception of febrile neutropenic cancer patients), and the new antibiotic policy was progressively applied for most infections possibly caused by Enterobacteriaceae; 3) during the post-intervention phase, piperacillin–tazobactam or ampicillin–sulbactam were preferred. The isolation policy did not change during the course of the study. Hand hygiene was reported to be performed throughout the study, but no further details were reported on how it was performed and whether compliance was assessed.

In Wen 2010 [59], the antibiotic changes took place in two phases: 1) infections were treated with conventional antibiotic therapy, and no changes in routine antibiotic intervention were made; 2) the use of third and fourth generation cephalosporins was restricted and replaced by 4.0 g piperacillin/0.5 g tazobactam (TZP) as first line therapy unless pathogenic bacteria were resistant. Other antibiotics were considered, e.g. for pregnant women and those whose condition may worsen due to TZP. In addition, antibiotics such as aminoglycosides, ciprofloxacin, vancomycin, teicoplanin, macrolides and carbapenems, were allowed.

Both studies reported statistically significant reductions in overall ESBL-E acquisition or prevalence after the change in antibiotic policy (39.8% pre-infection control measure versus 22.8% post-infection control measure, p=0.018 (56); [56]29.5% pre-infection control measure versus 19.5% post-infection control measure p=0.044 [59]). Neither study found significant reductions in ESBL-KP, but one reported a statistically significant reduction in ESBL-EC (25% pre-infection control measure versus 19.4% post-infection control measure, p<0.001 [56]).

The third single infection control measure study was a comparative study with two study arms (Prospero 2010 [50]). This study compared the incidence rates following an outbreak of ESBL-KP between two ICUs in Italy. One study arm used normal soap-based hand hygiene, the other one an alcohol rub. The authors reported a statistically significant difference in incidence density rates between the two ICUs, after the adoption of the alcohol rub (1.68/1 000 patient-days (95% CI 0.46, 4.31) versus 8.31/1 000 patient-days (95% CI 5.08, 12.84) with soap). Compliance with the infection control measure was measured based on alcohol hand rub consumption.

A summary of the findings from these studies is reported in Table 6.

Table 6. Summary of findings from the studies on single-facet infection control measures (three studies)

Study, location, study type	Infection control measures and compliance	Compliance assessed	Bacteria (outbreak-based or not)	Outcome measure	Baseline data (time period)	Follow-up data (time period)	Results of analysis
Lee 2007 [56] South Korea Before-and-after study	P (antibiotic formulary change – replacement of extended-spectrum cephalosporins with β-lactam/β-lactamase inhibitor combinations (piperacillin/tazobactam or ampicillin/sulbactam)	Yes: piperacillin/tazobactam in oncology ward increased (both, P for trend, 0.001); piperacillin/tazobactam in paediatric wards increased (P for trend, 0.001 and 0.002, respectively).	ESBL-EC and ESBL-KP (not an outbreak)	*Prevalence*: prevalence of ESBL producing organisms (individually and combined) across paediatric oncology and other paediatric wards.	*Prevalence* 41/103 (39.8%) All ESBL-E (all wards) 16/64 (25%) ESBL-EC 25/39 (64.1%) ESBL-KP Pre-infection control measure (1999–2001)	*Prevalence* 18/79 (22.8%) All ESBL-E (all wards) 7/36 (19.4%) ESBL(EC 11/43 (25.6%) ESBL(KP Post-infection control measure (2004–2005)	OR (95% CI, p-value from test for trend) for pre-infection control measure compared with post-infection control measure 2.24 (1.16- 4.32, p=0.018) All ESBL-E 5.20 (2.02- 13.40, p<0.001) ESBL-EC 1.38 (0.51- 3.76, p=0.514) ESBL-KP Results also reported for oncology ward; results showed a significant reduction in *K. pneumoniae* (p=0.029) only. For wards other than oncology there were significant reductions in ESBL-EC, ESBL-KP, individually and combined.
Prospero 2010 [56] Italy Controlled study	L (comparison of two ICUs with and without hand hygiene (alcohol rub))	Yes: but only amount of hand gel used reported, about 25 L/1000 patient days	ESBL-KP (outbreak)	*Incidence*: incidence density rate (IDR), colonisation rate per 1 000 patient days	*Incidence* 4.5/1 000 patient-days (95% CI 2.16-8.28) Pre-infection control measure ICU with hand rub 4.02/1 000 patient days (95% CI 1.93-7.40) Pre-infection control measure ICU without hand rub	*Incidence* 1.68/1 000 patient days (95% CI 0.46-4.31) Post-infection control measure ICU with hand rub 8.31/1 000 patient days (95% CI 5.08–12.84) Post-infection control measure ICU without hand rub	After the adoption of alcohol-based hand rub a significant difference in IDR was seen between the two ICUs (p-value NR) During the study, 79 patients had at least one ESBL-KP isolate, 60 of the patients had stays in one of the two ICUs

Study, location, study type	Infection control measures and compliance	Compliance assessed	Bacteria (outbreak-based or not)	Outcome measure	Baseline data (time period)	Follow-up data (time period)	Results of analysis
n 2010 [59] China Before-and-after study	P (antibiotic formulary change – replacement of third- and fourth-generation cephalosporins with piperacillin/ tazobactam)	Yes: 92.5% and 100% reduction in the use of third- and fourth-generation cephalosporins used in Phase IIb as compared with Phase I	ESBL-EC and ESBL-KP (not an outbreak)	*Acquisition rate:* patients negative at baseline (rectal swab, double disc test) but becoming positive during stay or at discharge; or being positive at baseline, negative, and then positive at discharge. *Baseline prevalence*: patients with positive rectal swab at baseline	*Acquisition rate* 39/132 (29.5%) ESBL-EC and ESBL-KP combined 36/132 (27.3%) ESBL-EC 7/132 (5.3%) ESBL-KP Phase I: pre-infection control measure *Baseline prevalence* 2/132 (1.5%) ESBL-EC and ESBL-KP combined 56/132 (42.4%) ESBL-EC 2/132 (1.5%) ESBL-KP	*Acquisition rate* 32/164 (19.5%) ESBL-EC and ESBL-KP combined 30/164 (18.3%) ESBL-EC 3/164 (1.8%) ESBL-KP Phase IIb: last 3 months of infection control measure *Baseline prevalence* 0/164 (0%) ESBL-EC and ESBL-KP combined 63/164 (38.4%) ESBL-EC 0/164 (0%) ESBL-KP	Acquisition rates of ESBL-EC and ESBL-KP combined, were significantly lower in Phase IIb than Phase I (p=0.044, chi-square test), however differences in each bacteria alone were slight and not significant (ESBL-EC p=0.065, ESBL-KP p=0.116). Specimens from infection sites were collected from 15 patients but no positive results for either bacterium were obtained in either phase.

L = hand hygiene, P = other (e.g. restrictions in antibiotic use), IDR = incidence density rate; ICU = intensive care unit

5.4 Multi-faceted studies

The remaining seven studies (Table 7) were multi-faceted and assessed the effects of implementing a bundle of infection control measures, which made it difficult to determine the influence and effectiveness of any one individual component of an infection control bundles – a fact acknowledged by several study authors. The most frequently included infection control measures in the bundles were: contact precautions (six studies), hand hygiene (six studies), and active surveillance during the outbreak (five studies). Most of the studies (six studies) also included other additional components, which have been described separately. The primary aim of three of the studies (Barbut 2013 [52], Johnson 2005 [54], Souweine 2000 [58]) was to monitor the transmission of MRSA and/or MREA; however, relevant data specifically relating to ESBL-E were also reported and are described below.

Table 7. Summary of infection control measures included in the multi-faceted studies to control the spread of ESBL-E

Infection control measure	No. of studies	Study IDs
Active screening on admission to hospital	0	-
Active screening on admission to specific ward/unit	4	Barbut 2013 [52], Laurent 2008 [55], Lucet 1999 [57], Souweine 2000 [58]
Pre-emptive isolation of patients on admission	4	Barbut 2013 [52], Lucet 1999 [57], Souweine 2000 [58], Laurent 2008 [55]
Contact tracing	0	-
Active surveillance during the outbreak	5	Barbut 2013 [52], Conterno 2007 [53], Laurent 2008 [55], Lucet 1999 [57], Souweine 2000 [58]
Patient cohorting	4	Barbut 2013 [52], Laurent 2008 [55], Lucet 1999 [57], Trick 2004 [51]
Patient isolation	5	Conterno 2007 [53], Lucet 1999 [57], Souweine 2000 [58], Trick 2004 [51], Laurent 2008 [55]
Nursing (or staff) cohorting	1	Laurent 2008 [55]
Dedicated nursing or other staff	1	Laurent 2008 [55]
Bathing with antiseptic agent	2	Johnson 2005 [54], Souweine 2000 [58]
Contact precautions	6	Conterno 2007 [53], Johnson 2005 [54], Laurent 2008 [55], Lucet 1999 [57], Souweine 2000 [58], Trick 2004 [51]
Hand hygiene	6	Barbut 2013 [52], Conterno 2007 [53], Johnson 2005 [54], Laurent 2008 [55], Lucet 1999 [57], Souweine 2000 [58]
Ward closure	0	-
Hospital closure	0	-
Patient record flagging	3	Conterno 2007 [53], Johnson 2005 [54], Lucet 1999 [57]
Environmental cleaning (including post discharge)	2	Conterno 2007 [53], Barbut 2013 [52]
Reinforced environmental cleaning of rooms after patient discharge	1	Laurent 2008 [55]
Nurse cohorting (dedicated nursing)	1	Laurent 2008 [55]
Other interventions: dedicated patient equipment; 'Operation Clean Start'[1]; alcohol-impregnated wipes for shared equipment; optimisation of bed occupancy; in-ward education for implementation of infection control measures [58]	4	Conterno 2007 [53], Johnson 2005 [54], Laurent 2008 [55], Souweine 2000 [58]

[1] *Operation Clean Start: for details please see Pittet et al. [60]*

Compliance with at least some of the specified infection control elements of the bundles was assessed in all but one study (Souweine 2000 [58]). However, even among those studies which reported compliance some elements of the infection control bundles were not assessed. This added to the difficulties of trying to determine the effectiveness of individual components within the infection control bundles.

A summary of the findings of the compliance assessments included in the studies on multi-faceted infection control bundles is reported in Table 8; details of the studies and their results are available in Table 9.

Table 8. Summary of compliance assessment in multi-faceted studies on the control of the spread of ESBL-E

Study	Compliance tested	Details (assessed measure and results of compliance assessment)
Barbut 2013 [52]	Yes	*Hand hygiene* – Amount of alcohol-based hand gel solution consumed increased significantly between 2007 and 2008: from 59.77 L/1000 patient-days) to 118.09 L/1000 patient-days (p<0.0001) and remained at a similar level in 2009 at 111.51 L/1000 patient-days (p=0.58). *Regular cleaning* – Significantly reduced mean bacterial surface counts from 2.9 to 0.1 cfu per 100cm^2 (p<0.001).
Conterno 2007 [53]	Yes	*Contact precautions* – 88% compliance overall, with significantly higher compliance among hospital staff (90%) compared with physicians (25%) (p< 0.001). *Hand hygiene* – compliance for patients not placed on contact precautions was only 47%, with significantly higher compliance among hospital staff (48%) compared with physicians (14%) (p< 0.001).
Johnson 2005 [54]	Yes	*Hand hygiene* – HCW hand hygiene compliance improved from a pre-infection control measure mean of 21% (95% CI, 20.3%–22.9%) to 42% (95% CI, 40.2%–43.8%) 12 months post-infection control measure (P<0.001); alcohol/chlorhexidine hand hygiene solution use increased from 5.7 to 28.6 L/1000 bed days.
Laurent 2008 [55]	Yes	*Hand hygiene* – Mean rate observed compliance rate was 70%, which was much higher than previously observed. *Changes to antibiotic formulary* – During the peak of the outbreak, the use of broad-spectrum antibiotics (e.g. ciprofloxacin, third- and fourth-generation cephalosporins, and meropenem) was lower than that observed during the 24 months before the outbreak, but most of the observed differences were not significant.
Lucet 1999 [57]	Yes	*Patient isolation procedures* – Increased from 57.5% to 79.2% in 1993 and from 71.0% to 93.5% in 1994. *Isolation door symbols* were used in 96% and 90% of observations in 1993 and 1994, respectively. Compliance with isolation procedures overall was observed in 11.4% of cases in 1993 and 50% in 1994. Breaks in the continuity of care recorded for 79 (74.5%) of 106 observations of contacts between ESBL-E-positive patients and healthcare workers in 1993, and for 4 (12.9%) of 31 in 1994 (p<0.0001). *Hand hygiene* – A significant increase in hand washing after contact with ESBL-E-negative patients was observed between 1993 and 1994 (p<0.0001).
Souweine 2000 [58]	No	Not assessed
Trick 2004 [51] (Two-armed study)	Yes	*Glove use* – The 'routine glove use' infection control measure group was significantly more likely to wear gloves (61% vs. 44%, p=0.03) and remove their gloves (97% vs. 77%, p=0.005). *Hand hygiene* – The 'routine glove use' infection control measure group was significantly more likely to adhere to hand hygiene (57% vs. 36%, p=0.02), and wear gloves or perform hand hygiene (71% vs. 52%, p=0.02) than the 'isolation precautions' infection control measure group.

HCW = healthcare worker; p = p-value; ICU = intensive care unit; L = litre; pt = patient; ESBL-E = extended-spectrum beta-lactamase-producing Enterobacteriaceae

Table 9. Summary of findings from infection control measures in multi-faceted studies on the control of the spread of ESBL-E (seven studies)

Study, location, study type	Infection control measures and compliance	Compliance assessed	Bacteria (outbreak-based or not)	Outcome measure	Baseline data (time period)	Follow-up data (time period)	Analysis results
Barbut 2013 [52] France Before-and-after study	B (type NR), C, E (type NR), F, L, Q (regular hydrogen peroxide vapour (HPV) disinfection of rooms, air disinfection of corridors, improved material storage)	Yes: hand hygiene (significant increase in alcohol-based hand gel 2007 and 2008 (p < 0.0001); similar level in 2009 (p=0.58)); regular cleaning (significant reduced mean bacterial surface counts (p<0.001))	ESBL-producing (NR other than ESBL-E) (not an outbreak)	*Incidence*: incidence of nosocomial and community-acquired ESBL-E cases in the pre-infection control measure and infection control measure time periods.	*Incidence* 1.2/1 000 patient-days Nosocomial ESBL-E 0.9/1 000 patient-days Community-acquired ESBL-E Pre-infection control measure (Dec 2006–Aug 2008)	*Incidence* 0.77/1 000 patient-days Nosocomial ESBL-E 1.15/1 000 patient-days Community-acquired ESBL-E During infection control measure (Sep 2008–Dec 2009)	A decrease in infections caused by ESBL-producing Enterobacteriaceae was seen during the infection control measure period but was not statistically significant (p=0.7 for nosocomial and also community-acquired cases). The main focus of the paper was the reduction of MRSA, which was significantly reduced (7.22 to 0.77 cases/1 000 patient-days).

Study, location, study type	Infection control measures and compliance	Compliance assessed	Bacteria (outbreak-based or not)	Outcome measure	Baseline data (time period)	Follow-up data (time period)	Analysis results
Conterno 2007 [53] Canada Before-and-after study	E (clinical culture), G, K, L, O, Q (thorough environmental cleaning, alert code added to electronic chart)	Yes: contact precautions - 88% compliance overall) and hand hygiene (only 14-48%)	ESBL-KP, ESBL-producing *K. oxytoca* and ESBL-EC) (not an outbreak)	*Incidence*: ESBL-E incidence (new cases), hospital and ICU-acquired cases. Regional Eastern Ontario ESBL-E rates were reported as a comparison.	*Incidence* 0.28/1 000 admissions (10 cases) New ESBL-E 0.03/1 000 patient-days (9 cases) Hospital-acquired 0.08/1 000 patient-days (1 case) ICU-acquired 1.32/100 000 (10 cases) Regional cases Pre-infection control measure (1999)	*Incidence* 0.67/1 000 admissions (30 cases) New ESBL-E 0.05/1 000 patient-days (19 cases) Hospital-acquired 0.12/1 000 patient-days (2 cases) ICU-acquired 9.28/100 000 (75 cases) Regional cases Post-infection control measure (2005)	Between 1999 and 2005 (infection control measure started Dec 2001) 122 new ESBL-E cases (66 *E. coli*, *12 K. oxytoca*, 44 *K. pneumoniae*) were detected with a significant increase over time (p≤0.001). The regional incidence also increased significantly during this time (p<0.0001). 92/122 cases were hospital-acquired and there was a significant increase (p=0.002). 15/92 cases were ICU-acquired and these increased from 0.46/1000 ICU days in 2001, then decreased to 0.12/1000 ICU days in 2005, a non-significant overall trend.
Johnson 2005 [54] Australia Before-and-after study	J, K, L, O, R (alcohol-impregnated wipes for shared equipment)	Yes: hand hygiene (significant improvement (P<0.001)	ESBL-EC and ESBL-producing *Klebsiella* spp. (not an outbreak)	*Rate:* rate of laboratory detection obtained from clinical specimens (retrospective analysis)	*Rate:* 0.55 isolates/100 patient discharges Pre-infection control measure (peak rate May 2001)	*Rate:* 0 isolates/100 patient discharges Post-infection control measure (Apr 2004) All isolates per patient were included, but screening swabs were excluded.	Total clinical isolates per month increased in the 28 months before the infection control measure (positive regression slope, p=0.006) but had fallen by >90% by month 36 of the infection control measure (negative slope, p<0.0001). The focus of the paper was MRSA but ESBL-E rates were also reported.
Laurent 2008 [55] Belgium Before-and-after study	B (rectal), C, E, F, G, H, I, K, L, P, Q, R (optimisation of bed occupancy)	Yes: hand hygiene (70%) and changes to antibiotic formulary (lower use but not significant)	ESBL-producing *K. pneumoniae* (outbreak)	*Incidence*: incidence rate of ICU-acquired colonisation or infection; incidence rate ratio (IRR) for after/during the outbreak; slope of the regression line for the number of hospital-acquired cases.	*Incidence* 6.86/1 000 patient—days *IRR* 15.1 Outbreak vs. baseline *Hospital-acquired* 0.97 (95% CI 0.39-1.56) Pre-infection control measure (during outbreak Jul–Nov 2005)	*Incidence* 0.08/1 000 patient—days *IRR* 0.11 After vs. outbreak *Hospital-acquired* -0.26 (95% CI -0.45–0.06) Post-infection control measure (Dec 2005–May 2006)	The baseline pre-outbreak incidence rate (Jan 2001–Jun 2005) was 0.44/1 000 patient-days. The peak incidence rate during the outbreak was 11.57/1 000 patient days. The outbreak affected 30 patients. The slopes of the regression lines were significantly different (p=0.001) before and after the infection control measure.
Lucet 1999 [57] France Before-and-after study	B (rectal swabs and urine specimens), C, E (rectal swabs and urine specimens), F, G, K, L, O, R (selective digestive decontamination in the first year)	Yes: patient isolation procedures (79.2% in 1993 and 93.5% in 1994); isolation door symbols (used in 96% [1993] and 90% [1994]) and hand hygiene (significant increase; p<0.0001)	ESBL-KP; ESBL-EC; ESBL-producing *Enterobacter* spp.; ESBL-producing other Entero-bacteriaceae (outbreak)	*Prevalence: numbers of imported, hospital-acquired, transferred ESBL-E-positive patients.* *Incidence rate: number of cases per 100 admissions*	*Prevalence:* 34 imported 173 hospital-acquired 90 transferred *Incidence:* 1.1/100 admissions imported 0.56/100 admissions hospital-acquired 1992 (infection control measure started Feb 1992)	*Prevalence:* 19 imported 19 hospital-acquired 27 transferred *Incidence:* 0.6/100 admissions imported 0.06/100 admissions hospital-acquired Post-infection control measure (1995)	The prevalence of imported cases (total 110) remained stable during the study. 30 were from ICUs, 20 medical/surgical wards, 19 nursing homes/rehabilitation units, 24 home and 10 from foreign countries. For hospital-acquired cases (total 328) there were highly significant reductions (p<0.0001 and 0.0035) from year to year.

Study, location, study type	Infection control measures and compliance	Compliance assessed	Bacteria (outbreak-based or not)	Outcome measure	Baseline data (time period)	Follow-up data (time period)	Analysis results
Souweine 2000 [58] France Before-and-after study	B (rectal), C, E (rectal or clinical), G, J, K, L, P	No	ESBL-producing producing *Klebsiella pneumoniae* (not an outbreak)	*Prevalence:* number of patients infected, and infected or colonised with *K. pneumoniae* *Incidence:* infection rate per 1 000 patient-days	*Prevalence* 3/29 (1.3%) infected 4/29 (1.7%) infected or colonised *Incidence* 1/1 000 patient-days Pre-infection control measure (May 1994–Apr 1995)	*Prevalence* 0/23 (0%) infected 0/23 (0%) infected or colonised *Incidence* 1/1 000 patient-days Post-infection control measure (May 1995–Apr 1996)	Numbers infected with *K. pneumoniae* pre- vs. post-infection control measure, p=0.06 (Fishers exact test). Numbers infected or colonised with *K. pneumoniae* pre- vs. post-infection control measure, p=0.025 (Fishers exact test). Also assessed MRSA and multidrug-resistant *Enterobacter aerogenes*.
Trick 2004 [51] USA Controlled study	Contact isolation group also F, G, K. Control group employed routine glove use.	Yes: glove use ('routine glove use' group significantly more likely to wear gloves (p=0.03), and remove their gloves (p=0.005); and hand hygiene ('routine glove use' group significantly more likely to adhere; p=0.02)	ESBL-KP (type 1, type 3 and NR) and ESBL-EC (not an outbreak)	*Acquisition:* number of patients who acquired a study organism (culture-negative at initial swab to positive by follow-up swap at discharge or at a point prevalence survey).	*Baseline prevalence* *K. pneumoniae* 19/114 (17%) Glove use 16/117 (14%) Contact isolation *E. coli* 29/114 (25%) Glove use 14/117 (12%) Contact isolation On initial swab	*Acquisition* *K. pneumoniae* 6/60 (10%) Glove use 12/72 (17%) Contact isolation *E. coli* 8/52 (15%) Glove use 8/76 (11%) Contact isolation Positive during study	Between group comparisons at baseline (Fisher exact or chi-squared test) *K. pneumoniae* p=0.5 *E. coli* p=0.009 Acquisition (RR (95% CI) contact isolation vs. glove use) K. *pneumoniae* 1.7 (0.7, 4.2) p=0.27 *E. coli* 0.7 (0.3, 1.7) p=0.41 Acquisition of Type I and Type 3 *K. pneumoniae* 2/60 (3.3%) glove use 9/72 (12%) isolation RR 3.8 (0.8, 17) p=0.06

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 staff, J = bathing in antiseptic, K = contact precautions, L = hand hygiene, M = ward closure, N = hospital closure, O =patient record flagging, P = antibiotic restriction or policy change, Q = environmental cleaning post-discharge, R =other

Two studies were linked to an outbreak, one by ESBL-KP in Belgium (Laurent 2008 [55]), the other by an unspecified ESBL-E in France (Lucet 1999 [57]). During the study by Laurent 2008 [55] the incidence reached a maximum of 11.57 cases per 1 000 patient-days and after implementation of reinforced measures, it dropped to 0.08 cases per 1 000 patient-days.

Five studies were not linked to an ESBL-E outbreak [51-54,58]. Only one comparative study (Trick 2004 [51]) involved a control group and reported a 'random' assignment of infection control measures. The measures were in fact not randomised and had a number of other methodological issues which may have affected the reliability of its findings. This study, which was conducted in a long-term care facility in the USA, compared contact isolation (a private or cohort room with gowns and gloves available at the entrance; residents were not confined to their room) with routine glove use. Healthcare workers were assigned to one of the two units and cross-over was infrequent. There was no significant difference between the two units in the acquisition of ESBL-KP (11% contact isolation versus 15% glove use, p=041) or ESBL-EC (17% contact isolation versus 10% glove use, p=0.27). The acquisition ESBL-KP strains was higher in residents in the contact isolation unit, but not significantly so (p=0.06, nine versus two cases).

Two studies (Barbut 2013 [52] and Conterno 2007 [53]) assessed environmental cleaning (also with hydrogen peroxide vapour disinfection) alongside other components, including active screening/surveillance, hand hygiene, patient cohorting and record flagging. Both assessed compliance with hand hygiene, one with regular cleaning (Barbut 2013 [52]) and one with contact precautions (Conterno 2007 [53]). Neither found a significant decrease in ESBL-E infections as a result of the infection control measure. One study (Barbut 2013 [52]), conducted in France, reported a decrease in infections caused by ESBL-E during the infection control measure, but this was not statistically significant (p=0.7 for both nosocomial and community-acquired cases). Conterno 2007 [53] was conducted in Canada and reported significant increases in new ESBL-E (ESBL-KP and ESBL-EC) cases over time after the infection control measure had started (p≤0.0001). The regional ESBL-E incidence, however, had increased seven-fold, as had the number of imported ESBL-E cases during the same time period (p≤0.0001). Although there was no reduction in the rates of nosocomial ESBL-E, the fact that rates of nosocomial ESBL-E showed only a minimal increase – despite a strong regional increase and influx of ESBL-E into the hospital – was

considered a display of the effectiveness of the applied infection control measures. Also reported was an increase in ICU-acquired cases, followed by a decrease, but this was statistically not significant.

An Australian study (Johnson 2005 [54]) evaluated a three-year programme covering antiseptic bathing, contact precautions, hand hygiene, patient-record flagging, and a detailed educational and promotional package. Measures were aimed at controlling MRSA, but ESBL-E results were also reported. Compliance with hand hygiene was measured and improved significantly. The rate of ESBL-EC and ESBL-producing *Klebsiella* species detected per month significantly increased in the 28 months before the infection control measures ($p=0.006$) but fell by more than 90% at 36 months after the introduction of infection control measures ($p<0.0001$), a reduction which was statistically significant.

A French study (Souweine 2000 [58]) evaluated a wide-range of infection control measures covering screening and pre-emptive isolation on admission, active surveillance, patient isolation, antiseptic bathing, contact precautions, hand hygiene and discouragement of imipenem as an empiric antibiotic treatment. Compliance with the infection control measures was not assessed. The study reported a significant reduction in the numbers of patients infected or colonised with ESBL-KP (1.3% pre-infection control measure to 0% post-infection control measure, $p=0.025$). There was no significant change in the number of patients infected with ESBL-KP (1.3% versus 0%, $p=0.06$) although this may be due to the small size of the study (29 patients pre- and 23 patients post-infection control measure). The study reports that 16 patients were placed in isolation on admission because they had been referred from another ICU; two patients remained in isolation as they were positive for MRSA, ESBL-E or MREA.

5.5 Summary of evidence to support individual infection control measures

The following section summarises the evidence available from the 10 included studies in order to support the effectiveness of each of the reported individual infection control measures. However, given the limited quality of a number of the studies (even the comparative studies with a control group) and the fact that interventions were part of a bundle of infection control measures, these summaries should be interpreted with caution and are at best suggestive of a benefit. However, further research is required before definitive statements can be made.

5.5.1 Active screening on admission to specific ward/unit

Four studies, all before-and-after study designs, reported active screening for ESBL-E on admission as part of a bundle of measures (Barbut 2013 [52], Laurent 2008 [55], Lucet 1999 [57], Souweine 2000 [58]). The source of the cultures was not identified in one study (Barbut 2013 [52]) and involved the use of rectal cultures in the other studies (Laurent 2008 [55], Lucet 1999 [57], Souweine 2000 [58]). None of the studies assessed active screening on admission in isolation from other infection control measures, and none of the studies assessed compliance with this specific measure. One study failed to find any statistically significant change in either nosocomial or community-acquired ESBL-E (Barbut 2013 [52]). The other studies (Laurent 2008 [55], Lucet 1999 [57], Souweine 2000 [58]) all reported statistically significant reductions after the implementation of the infection control measure. Two studies assessed numbers of hospital-acquired ESBL-E. Of these, one French outbreak study did not report the ESBL-E type (Lucet 1999 [57]). Laurent 2008 [55], a Belgian outbreak study, assessed levels of ESBL-KP. The third study, also from Belgium, assessed the number of patients infected or colonised with ESBL-KP (Souweine 2000 [58]).

In summary, there is evidence from studies on infection control bundles to suggest that active screening (rectal) for ESBL-E on admission to a specific ward/unit is effective for limiting and preventing the spread of ESBL-E, at least with respect to ESBL-KP (evidence level ++).

5.5.2 Pre-emptive isolation of patients on admission

Four studies (Barbut 2013 [52], Lucet 1999 [57], Laurent 2008 [55] and Souweine 2000 [58]), all before-and-after study designs, included pre-emptive patient isolation on admission as part of an infection control bundle. None of the studies assessed the effects of this specific measure in isolation from the other control measures in the bundle, and only one study assessed compliance with isolation measures (Lucet 1999 [57]), which appeared to be ≤50%. One French study (Barbut 2013 [52]) did not find any statistically significant change in either nosocomial or community-acquired ESBL-E during an outbreak. The other two studies reported some statistically significant reductions after the implementation of infection control measures. One French study assessed hospital-acquired ESBL-E during an outbreak (ESBL-E type not reported; Lucet 1999 [57]); and another study (Souweine 2000 [58]), also from France, assessed the number of patients infected or colonised with ESBL-KP.

In summary, there is evidence from studies of infection control bundles to suggest that pre-emptive patient isolation on admission is effective for limiting and preventing the spread of ESBL-E, at least with respect to ESBL-KP (evidence level ++).

5.5.3 Active surveillance during an outbreak

Five studies, all with before-and-after study designs, reported the implementation of active surveillance during an outbreak as part of a bundle of infection control measures (Barbut 2013 [52], Conterno 2007 [53], Laurent 2008 [55], Lucet 1999 [57], Souweine 2000 [58]). The source of the cultures was not identified in Barbut 2013 [52]; in the three other studies (Laurent 2008 [55], Lucet 1999 [57], Souweine 2000 [58]) rectal cultures were used and Conterno 2007 [53] used clinical specimens. None of the studies examined the effects of this specific intervention in isolation from other infection control measures and none assessed compliance with the measure. One French study did not find any statistically significant change in either healthcare-associated or community-acquired ESBL-E (type NR) (Barbut 2013 [52]). Two studies reported significant reductions in hospital-acquired ESBL-E; one French outbreak study failed to report the ESBL type (Lucet 1999 [57]). Another study reported a reduction in the numbers of patients infected or colonised with ERSBL-KP (Souweine 2000 [58]). However, a Canadian study reported a significant increase in the number of new and hospital-acquired ESBL-E cases (ESBL-KP, ESBL-producing *K. oxytoca* and ESBL-EC) and a non-significant overall trend in the number of ICU-acquired cases (Conterno 2007 [53]) during the infection control measures.

In summary, there is evidence from studies on infection control bundles to suggest that active surveillance (including rectal and other cultures) is effective in limiting and preventing the spread of ESBL-E, at least with respect to ESBL-KP (evidence level ++).

5.5.4 Patient cohorting

Four studies reported the implementation of patient cohorting as an infection control measure during an outbreak (Barbut 2013 [52], Laurent 2008 [55], Lucet 1999 [57], Trick 2004 [51]). None of the studies specifically assessed compliance with this measure. One US study (Trick 2004 [51]) used a comparative design to compare contact isolation with routine glove use and included patient cohorting in the contact isolation group. However, no significant differences in the acquisition of ESBL-EC and ESBL-KP were found between the two intervention groups. The remaining studies were all before-and-after studies (Barbut 2013 [52], Laurent 2008 [55], Lucet 1999 [57]). One study from France did not find any statistically significant change in either nosocomial or community-acquired ESBL-E (type NR) (Barbut 2013 [52]). Two studies reported significant reductions in hospital-acquired ESBL-E; one French outbreak study did not report the ESBL-E type (Lucet 1999 [57]). Laurent 2008 [55] assessed ESBL-KP during an outbreak in Belgium.

In summary, there is evidence from studies on infection control bundles to suggest that patient cohorting is effective for limiting and preventing the spread of ESBL-E, at least with respect to ESBL-KP (evidence level ++). Although this evidence supports this infection control measure, the findings are not consistent throughout all the studies. Studies of better methodological and reporting quality are required to enhance these findings.

5.5.5 Patient isolation

Five studies (Conterno 2007 [53], Lucet 1999 [57], Souweine 2000 [58], Trick 2004 [51], Laurent 2008 [55]) assessed patient isolation as an infection control measure, but only Lucet 1999 [57] also assessed compliance with this intervention. This study found only up to 50% compliance with the isolation procedures overall and also reported breaks in the continuity of care for up to 74.5% of ESBL-E-positive patients. One of the studies, a controlled study from the USA, examined patient isolation as the primary infection control measure (Trick 2004 [51]). This comparative study found no significant differences between a contact isolation unit and routine glove use in the acquisition of ESBL-EC and ESBL-KP. The other four studies were all before-and-after studies, which reported patient isolation as a part of an infection control bundle (Conterno 2007 [53], Lucet 1999 [57], Souweine 2000 [58], Laurent 2008 [55]). Three studies, two from France [57,58] and one from Belgium [55], reported significant reductions in colonisation and/or infections; two were conducted during an outbreak (Lucet 1999 [55,57]). However, one study from Canada reported a significant increase in the number of new and hospital-acquired ESBL-E cases (ESBL-KP, ESBL-producing *K. oxytoca* and ESBL-EC) during the infection control measure and a non-significant overall trend in the number of ICU-acquired cases (Conterno 2007 [53]).

In summary, there is evidence from studies of infection control bundles to suggest that patient isolation is effective for limiting and preventing the spread of ESBL-E, at least with respect to ESBL-KP (evidence level ++). Although the evidence supports this infection control measure, the findings are not consistent throughout all studies. Studies of better methodological and reporting quality are required to support these findings.

5.5.6 Bathing with antiseptic agents

Two before-and-after studies (Johnson 2005 [54], Souweine 2000 [58]) assessed antiseptic bathing or washes, as part of an infection control bundle. Neither of the studies assessed the effects of this measure in isolation from the other infection control measures in the bundle, and neither assessed compliance. In one study, chlorhexidine was used (Souweine 2000 [58]); another used mupirocin and triclosan body washes (Souweine 2000 [58]). Both studies were performed under non-outbreak conditions and reported statistically significant reductions in ESBL-E. One study from Australia found a reduction in the number of ESBL-EC and ESBL-producing *Klebsiella* isolates

detected per month (Johnson 2005 [54]), a study from France found reductions in the number of patients infected or colonised with ESBL-KP (Souweine 2000 [58]).

In summary, there is evidence from studies of infection control bundles to suggest that antiseptic bathing/washing is effective for limiting and preventing the spread of ESBL-E, at least with respect to ESBL-KP (evidence level ++).

5.5.7 Contact precautions

Six studies (Conterno 2007 [53], Johnson 2005 [54], Laurent 2008 [55], Lucet 1999 [57], Souweine 2000 [58], and Trick 2004 [51]) implemented contact precautions. Only one study (Trick 2004 [51]) looked at the effects of this measure by performing an intervention study on routine glove use alone. In all other studies, however, contact precautions were not assessed in isolation from other measures in an infection control bundle. Only two studies specifically assessed compliance with this intervention (Conterno 2007 [53] and Trick 2004 [51]); Conterno 2007 [53] reported 88% compliance overall. Trick 2004 [51] used a comparative design, comparing isolation to routine glove use (incorporating contact precautions) and found no significant differences between the two intervention groups in the acquisition of ESBL-EC and ESBL-KP. The remaining five studies (Conterno 2007 [53], Johnson 2005 [54], Laurent 2008 [55], Lucet 1999 [57], Souweine 2000 [58]) all used a before-and-after design. Two of these studies were carried out during outbreaks (Laurent 2008 [55], Lucet 1999 [57]). Four before-and-after studies reported statistically significant reductions: one French study where the species of ESBL-E was not reported (Lucet 1999 [57]), one from Belgium reporting ESBL-KP (Laurent 2008 [55]), one from Australia reporting a reduction in the number of ESBL-EC and ESBL-producing *Klebsiella* isolates (Johnson 2005 [54]), and a study from France which reported a reductionin infections and colonisation with ESBL-KP (Souweine 2000 [58]). A Canadian study reported significant increases in the numbers of new and hospital-acquired ESBL-E cases (ESBL-KP, ESBL-producing *K. oxytoca* and ESBL-EC) during the infection control measure and a non-significant overall trend in the number of ICU-acquired cases (Conterno 2007 [53]).

In summary, there is evidence from studies of infection control bundles to suggest that contact precautions are effective for limiting and preventing the spread of ESBL-KP and ESBL-EC (evidence level ++).

5.5.8 Hand hygiene

One single-facet study (Prospero 2010 [50]) and six multi-faceted studies (Barbut 2013 [52], Conterno 2007 [53], Johnson 2005 [54], Laurent 2008 [55], Lucet 1999 [57], and Souweine 2000 [58]) reported the implementation of hand hygiene as an infection control measure. Six studies assessed compliance with hand hygiene, which, where reported, did not always appear to be optimal (Conterno 2007 [53], Johnson 2005 [54]). The types of hand wash reported included alcohol (Barbut 2013 [52], Laurent 2008 [55], Prospero 2010 [50]), antiseptic soap (Lucet 1999 [57]), clorhexidine (Souweine 2000 [58]), and alcohol/chlorhexidine (Johnson 2005 [54]). The one single-facet study (Prospero 2010 [50]) compared the incidence of ESBL-KP in two intensive care units, with and without the use of alcohol hand-rub, and found a significantly lower incidence of ESBL-KP in the unit which used this. In all six multi-faceted studies, hand hygiene was reported as part of an infection control bundle. Four of these studies (Johnson 2005 [54], Lucet 1999 [57], Laurent 2008, Souweine 2000 [58]) reported statistically significant reductions. Two studies (Lucet 1999 [57], Laurent 2008 [55]) found reductions in hospital-acquired ESBL-E. Lucet 1999 [57], however, did not report the ESBL-E species. Laurent 2008 [55] examined an ESBL-KP outbreak in Belgium. An Australian study recorded the number of ESBL-EC and ESBL-producing Klebsiella isolates detected per month (Johnson 2005 [54]). Another study found a reduction in the numbers of patients infected or colonised with ESBL-KP (Souweine 2000 [58]). One outbreak study from France did not find any statistically significant change in either nosocomial or community-acquired ESBL-E (Barbut 2013 [52]), despite a significant increase in the use of alcohol hand rub. A study from Canada reported significant increases in the numbers of new and hospital-acquired ESBL-E cases (ESBL-KP, ESBL-producing K. oxytoca and ESBL-EC) during the infection control measure and a non-significant overall trend in the number of ICU-acquired cases (Conterno 2007 [53]). The study rated hand hygiene compliance as suboptimal (47%).

In summary, there is evidence – strengthened by evidence from a single-faceted study – to suggest that hand hygiene, particular if alcohol-based products are used – is effective in the control of the spread of ESBL-E (evidence level ++).

5.5.9 Patient record flagging

Three before-and-after studies (Conterno 2007 [53], Johnson 2005 [54], Lucet 1999 [57]) reported patient record flagging as an infection control measure (part of a bundle). None of the studies assessed patient record flagging in isolation from other measures in the infection control bundles, and none assessed compliance. Two of the studies (Johnson 2005 [54], Lucet 1999 [57]) reported statistically significant reductions. These included an outbreak study (Lucet 1999 [57]) carried out in France, which found a reduction in hospital-acquired ESBL-E (type not reported), and a study by Johnson 2005 [54] from Australia, which reported a reduction in the number of ESBL-EC and ESBL-producing *Klebsiella* isolates detected per month. A Canadian study (Conterno 2007 [53]) found significant increases in the number of new and hospital-acquired ESBL-E cases (ESBL-KP, ESBL-producing

K. oxytoca and ESBL-EC) during the infection control measure and a non-significant overall trend in the number of ICU-acquired cases.

In summary, there is evidence from studies of infection control bundles to suggest that patient record flagging is effective in limiting and preventing the spread of ESBL-KP and ESBL-EC (evidence level ++).

5.5.10 Antibiotic formulary changes and restriction policies

Two single-facet studies (Lee 2007 [56], Wen 2010 [59]) used a before-and-after design looking at antibiotic policy changes, and both studies reported high compliance. The studies, one conducted in Korea, one in China, also reported statistically significant reductions either in the healthcare-associated acquisition or prevalence of ESBL-E after the change in policy. The study from South Korea also found a statistically significant reduction in ESBL-EC (Lee 2007 [56]). Neither study found a change in healthcare-associated acquisition or prevalence of ESBL-KP.

In summary, there is evidence – also from studies of single infection control measures – to suggest that antibiotic policy changes are effective in controlling the spread of ESBL-E although this may be limited to the control of ESBL-EC rather than ESBL-KP (evidence level ++).

5.5.11 Environmental cleaning (including post-discharge)

Two before-and-after studies [52,53] included environmental cleaning after patient discharge as part of an infection control bundle. Neither study assessed the effects of environmental cleaning in isolation from the other measures in the infection control bundle. One of the studies (Barbut 2013 [52]) assessed compliance with cleaning and reported that it significantly reduced surface bacterial counts. One study (Barbut 2013 [52]) used regular hydrogen peroxide vapour room disinfection as well as air disinfection of corridors; although there was a 36% decrease in the rate of nosocomial ESBL-E, this was statistically not significant. The second study (Conterno 2007 [53]) included thorough environmental cleaning and reported only a marginal increase in nosocomial rates, despite the seven-fold regional increase in ESBL-E incidence and an increase in cases imported to the hospital. Significant increases in the number of new and hospital-acquired ESBL-E cases (ESBL-KP, ESBL-producing *K. oxytoca* and ESBL-EC) were reported during the implementation period of this infection control measure. A non-significant overall decreasing trend in the number of ICU-acquired cases was also reported.

In summary, there is no evidence to suggest that environmental cleaning is effective in controlling the spread of ESBL-KP and ESBL-EC (evidence level ++).

5.5.12 Reinforced environmental cleaning of rooms after patient discharge

One before-and-after study (Laurent 2008 [55]) conducted during an outbreak in Belgium included reinforced cleaning of rooms after patient discharge; the study reported a statistically significant reduction in hospital-acquired ESBL-KP.

Although this evidence supports this infection control measure, findings are based on only one study. More studies of better methodological and reporting quality are required to augment these findings.

In summary, there is evidence to suggest that reinforced cleaning of rooms on patient discharge is effective for reducing hospital-acquired ESBL-KP (evidence level ++).

5.5.13 Nurse cohorting (dedicated nursing)

One before-and-after study (Laurent 2008 [55]) included a nurse cohorting unit with dedicated nursing staff which reported a statistically significant reduction in hospital-acquired ESBL-KP during an outbreak in Belgium.

Although this evidence supports this infection control measure, the findings are based on a small number of studies. More studies and studies of better methodological and reporting quality are required to enhance these findings.

In summary, there is evidence to suggest that nurse cohorting with dedicated nursing staff is effective for reducing hospital-acquired ESBL-KP (evidence level ++).

5.5.14 Other

Additional interventions were reported in the included studies as part of the infection control bundles and were only mentioned with no further reporting or analysis. For this reason, no conclusions can be drawn from these interventions, but they are mentioned here for completeness' sake (see Table 2): a) dedicated patient equipment [53], b) 'Operation Clean Start' [54,60], c) alcohol-impregnated wipes for shared equipment [54], d) optimisation of bed occupancy [55], and e) in-ward education on the implementation of infection control measures [58].

6 Discussion

This systematic review sought to provide an up to date summary of the best available evidence regarding the use of infection control measures to control the transmission and spread of ESBL-E through patient transfer between healthcare facilities, with special emphasis on cross-border transfer. Given the lack of infection control measures specifically targeting the cross-border transfer of patients, this review also includes studies that assess any infection control measure aimed at preventing ESBL-E transmission, both within and between healthcare settings of any type.

6.1 Summary of main findings

In total, 5 155 records (after deduplication in EndNote) were retrieved, and 186 full papers were screened in further detail. Of these, 97 separate studies (reported in 104 full text articles) met the inclusion criteria for this review. Of these, 10 studies (reported in 10 full text articles) were selected as representing the best available evidence and analysed in detail.

Half of the studies were conducted in Europe (Barbut 2013, [52] Laurent 2008, [55] Lucet 1999, [57] Prospero 2010, [50] Souweine 2000 [58]). All of the studies were set in acute care hospitals, with the majority involving adult populations and only one a paediatric population (Lee 2007 [56]).

The overall quality of the 10 studies included in the analysis was at best moderate. In terms of the hierarchy of evidence, the two comparative studies (Prospero 2010 [50], Trick 2004 [51]) represented a higher level of evidence than the remaining eight studies, which used a before-and-after design. However, methodological deficiencies were apparent in all of the studies, limiting the reliability of their findings.

Three of the included studies assessed single-facet infection control measures. All of the studies assessed compliance with the prescribed infection control measures. Two Asian, quasi-experimental/before-and-after studies assessed the effects of a change in antibiotic policy unrelated to outbreaks (Lee 2007 [56], Wen 2010 [59]). Both involved the replacement of cephalosporins with a piperacillin–tazobactam combination or an ampicillin–sulbactam combination. The studies reported statistically significant reductions in overall ESBL-E acquisition or prevalence after the change in antibiotic policy (39.8% pre-infection control measure versus 22.8% post-infection control measure, p=0.018; 29.5% pre-infection control measure versus 19.5% post-infection control measure p=0.044, respectively). Neither found significant reductions in ESBL-KP; one study reported a statistically significant reduction in ESBL-EC (25% pre-infection control measure versus 19.4% post-infection control measure, p<0.001). The third single-facet infection control measure study (Prospero 2010 [50]) compared incidence rates following an outbreak of ESBL-KP between two infection control arms (hand washing with alcohol versus soap) carried out in Italian ICUs. The authors reported a statistically significant difference in incidence density rates between the study arms, after the adoption of the alcohol rub (1.68/1 000 patient-days (95% CI 0.46, 4.31)) versus soap (8.31/1 000 patient-days (95% CI 5.08, 12.84)).

The remaining seven studies assessed the effects of introducing a bundle of infection control measures. The primary aim of Barbut 2013 [52], Johnson 2005 [54], and Souweine 2000 [58] was to monitor the transmission of MRSA and/or MREA, but they also reported relevant data relating to ESBL-E. Compliance with at least some of the specified infection control elements of the infection control bundles was assessed in all but one study (Souweine 2000 [58]). However, even among the studies which assessed compliance, some elements of the infection control bundle were not assessed. This added to the difficulties in trying to determine the effectiveness of individual components within the infection control bundles. Only one comparative study (Trick 2004 [51]) was identified, and even this study suffered from a number of other methodological issues which may have affected the reliability of its findings. Trick 2004 [51] compared contact isolation with routine glove use. No significant difference was found between the two study arms in the acquisition of ESBL-KP (11% contact isolation versus 15% glove use, p=041) or ESBL-EC (17% contact isolation versus 10% glove use, p=0.27). However, the acquisition of ESBL-KP strains was higher in residents in the contact isolation unit, but not significantly so (p=0.06, nine versus two cases).

The limited quality of most studies (even those using a controlled study design) and the use of multi-faceted infection control measures limited the interpretation of data. However, there was evidence to suggest that the following measures may limit the spread of some types of ESBL-E: active screening on admission to specific ward/unit (four studies), pre-emptive isolation of patients on admission (four studies), active surveillance during the outbreak (five studies), patient isolation (five studies), patient cohorting (four studies), bathing in antiseptic (two studies), contact precautions (six studies), hand hygiene (seven studies), patient record flagging (three studies), and antibiotic formulary change (two studies). The only other potentially effective infection control measure (nurse cohorting in a specific unit) was assessed in only one study. No evidence of the beneficial effects of environmental cleaning was identified. Possibly the best evidence of a beneficial effect was related to changes to the local antibiotic policy. However, these findings should be interpreted with caution and are only suggestive of potential benefits.

6.2 Comparisons with other research

At the time of the literature search for this review, three systematic reviews published between 2009 and 2011 were identified, which also sought to assess the effectiveness of infection control measures to control the spread of ESBL-E.

The first systematic review by Goddard 2011 [61] examined the efficacy of ESBL-E infection control measures in hospitals during a non-outbreak setting. The review included four uncontrolled, retrospective studies published between January 1985 and April 2010 (Conterno 2007, [53] Johnson 2005, [54] Souweine 2000 [58] and Soulier 1995 [62]). Except for Soulier 1995 [62] – related to Barbut 1994 [63] –, all studies were included in our review. Soulier 1995 [62] was excluded from this review because did not reported in sufficient detail. The conclusions in Goddard 2011 [61] are similar to the ones in this review in that the study also identified a lack of well-designed prospective studies. The authors went on to stress the urgent need for research in this area.

Kramme 2009 [64] carried out a systematic review of infection control measures implemented to control outbreaks with multidrug-resistant gram-negative bacteria. This review was only published as an abstract and, therefore, few details are available. In this review 27 articles published between 2000 and 2009 were included, describing the use of infection control measures in 25 outbreaks. The lack of controlled studies was again highlighted by the authors who reported that the most commonly used infection control measures included: 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%). In our review, the two studies featuring environmental cleaning as part of a bundle of infection control measures failed to find any significant beneficial effect, but active surveillance, single/cohort isolations and changes to antimicrobial use recommendations did appear to be potentially beneficial, although the evidence was less than optimal.

The third systematic review by Zhuchenko 2011 [65,66] assessed nosocomial outbreaks caused by multidrug-resistant gram-negative bacteria. The authors used a risk factor analysis to identify factors associated with the outbreaks. Data from a total of 57 ESBL-E outbreaks was included, and outbreaks appeared to be significantly associated with reductions in the use of isolation precautions, and less frequently associated with the closure of wards and the use of protective clothing.

Although numerous websites and publications mention methods for the control of ESBL-E transmission, few up-to-date guidelines/recommendations have been published with specific reference to infection control measures for the prevention of ESBL-E transmission. A notable exception are the 2014 guidelines published by the European Society of Clinical Microbiology and Infectious Diseases [40].

Studies of infection control measures for MDROs such as CPE may also be relevant for the control of ESBL-E, given the similarities in the transmission sources and routes. Therefore, a related systematic review [67], carried out for ECDC in tandem with this review, may provide relevant information regarding potential infection control measures, although this review was also subject to limitations with respect to the quantity and quality of the available evidence. Similarly, guidelines on infection control measures for MDROs and CPE may also offer some relevant advice for the control of ESBL-E, for example the 'Guidelines for the control of MDROs' published in 2006 by the US Centers for Disease Control and Prevention [41] and the 2014 guidelines published by the European Society of Clinical Microbiology and Infectious Diseases published [40] .

6.3 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 no miss any important data, 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 on the use of measures to control of ESBL-E transmission. However, when screening the titles/abstracts for inclusion in the review, full articles were ordered when there were doubts about relevance. In addition, studies professing to evaluate the control of MRSA/MREA (Barbut 2013 [52], Johnson 2005 [54], Souweine 2000 [58]) and without any mention of ESBL-E infection control measures in the title or abstract were identified as containing relevant ESBL-E data collected during ESBL-E outbreaks.

The methodological quality of studies often limits the scientific value of a systematic review. In this review, we sought to limit our analysis 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, were limited. Two controlled studies were identified in this review, but neither was judged to be of good quality when assessed using a tool specifically designed to assess the risk of bias in controlled studies.

The majority of the studies used designs where the incidence/prevalence of ESBL-E was assessed before, during and after the implementation of an infection control measure. This type of study design is subject to a number of biases, including the risk of confounding. The studies also tended to investigate bundles of infection control measures introduced at a single time point, which precluded any assessment of the contribution of individual components. Similarly, only infection control measures that changed between the pre- to post-infection control measure periods were considered to be associated with any change in the level of transmission or spread of ESBL-E. 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, known as 'Hawthorne effect' or 'observer effect', a well-documented effect for infection control measures, e.g. hand hygiene [68,69].

The studies were also heterogeneous, particularly with respect to populations, infection control measures, outcomes and outcome 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 [1]. In particular, infection control measures, outcomes, and outcome assessment methods (i.e. laboratory tests and tests for the detection of specific ESBLs types) were poorly described in many of the studies identified in this review. 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.

6.4 Recommendations for further research

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

- Further research in this topic area and on the interventional components identified in this review: active screening on admission to specific ward/unit, pre-emptive isolation of patients on admission, active surveillance during the outbreak, patient cohorting, patient isolation, bathing with antiseptic agents, contact precautions, hand hygiene, patient record flagging, and antibiotic formulary change.
- 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).

6.5 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).

7 Conclusions

In this review, the following statements regarding the evidence for the effectiveness of infection control measures in reducing the rates of ESBL-E colonisation and/or infection can be made:

- No evidence was identified for infection control measures that were specifically implemented for the prevention of transmission of ESBL-E through cross-border transfer. Two studies, however, did report on the effectiveness of infection control measures implemented for imported cases of ESBL-E, including cases transferred within the same hospital. There is evidence that infection control measures are effective in reducing the spread of ESBL-E from cases imported into healthcare settings (evidence level ++).
- There is evidence, including evidence from single facet studies, for the effectiveness of antibiotic formulary changes and antibiotic restriction policies (evidence level ++).
- There is evidence from studies that report multi-faceted infection control bundles for the effectiveness of early implementation of: a) active surveillance (screening) by rectal screening for ESBL-E carriage on admission to specific wards/units, b) pre-emptive isolation of high-risk patients upon admission and c) active surveillance during outbreaks (evidence level ++).
- There is evidence from studies that report multi-faceted infection control bundles that the following infection control measures are effective: a) hand hygiene, b) contact precautions (gloves and gowns), c) patient cohorting, d) patient isolation, e) case notification/patient record flagging, f) bathing with antiseptic agents, g) nurse (or staff) cohorting (equivalent to dedicated nursing), h) antibiotic restriction policies, and i) reinforced environmental cleaning post patient discharge (evidence level ++).
- In these reviews, the best available evidence for the effectiveness of infection control interventions 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 ESBL-E.

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Appendix 1. Search strategies

EMBASE (OvidSP): 1974-2013/07/02
Searched 10 July 2013

1 extended spectrum beta lactamase producing enterobacteriaceae/ (497)
2 (ESBL-E or ESBLE).ti,ab,ot. (209)
3 (extend$ adj2 spectrum adj2 (beta or "B") adj2 lactam$ adj3 enterobacter$).ti,ab,ot. (784)
4 or/1-3 (1278)
5 extended spectrum beta lactamase/ (4178)
6 (extend$ adj2 spectrum adj2 (beta or "B") adj2 lactam$).ti,ab,ot. (6117)
7 (ESBL or ESBLs).ti,ab,ot. (5438)
8 or/5-7 (8286)
9 enterobacteriaceae/ or exp citrobacter/ or exp enterobacter/ or exp escherichia/ or exp hafnia/ or exp klebsiella/ or exp kluyvera/ or exp morganella/ or exp proteus/ or exp providencia/ or exp serratia/ (332883)
10 enterobacteriaceae infection/ or exp *Escherichia coli* infection/ or exp klebsiella infection/ or exp proteus infection/ or exp serratia infection/ (7328)
11 (enterobacter$ 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. (306324)
12 (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. (9128)
13 or/9-12 (406293)
14 8 and 13 (7059)
15 4 or 14 (7148)
16 infection control/ or infection prevention/ or soap/ or exp face mask/ or mask/ or surgical mask/ or cross infection/pc (113548)
17 hand washing/ or antisepsis/ or mandatory testing/ (11740)
18 protective clothing/ (9605)
19 hospital hygiene/ (2027)
20 (Infection$ adj2 (control$ or prevention or prophyla$)).ti,ab,ot. (32194)
21 (handwash$ or handscrub$ or handrub$).ti,ab,ot. (1673)
22 ((hand or hands) adj2 (wash$ or clean$ or sanit$ or scrub$ or hygien$ or steril$ or gel or gels or sanitiz$ or sanitis$)).ti,ab,ot. (6257)
23 (soap$ 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$).ti,ab,ot. (81651)
24 (alcohol adj3 (gel or gels or wash$ or hand-rub$)).ti,ab,ot. (983)
25 (protective cloth$ or protective$ equipment$ or PPE or glove$ or gown$ or facemask$ or faceshield$ or mask$ or face shield$ or apron$ or face mask$).ti,ab,ot. (77328)
26 (barrier$ adj2 (nurs$ or precaution$)).ti,ab,ot. (871)
27 ((nurs$ or patient$ or inpatient$) adj2 (separat$ or isolat$ or segrat$)).ti,ab,ot. (32397)
28 (cohorted or cohorting or quarantin$ or "cohort nursing").ti,ab,ot. (3389)
29 ((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 "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$)).ti,ab,ot. (7615)
30 ((antibiotic$ or anti-biotic$ or antimicrobial$ or anti-microbial$) adj2 (class shift or restrict$ or limit$ or reduc$ or minimi$)).ti,ab,ot. (4365)
31 screening/ or feces analysis/ (111918)
32 (screen$ 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$).ti,ab,ot. (1158558)
33 ((faeces or feces or faecal$ or fecal$ or rectal$ or rectum or stool or bowel movements$) adj2 (test$ or swab$ or specimen$ or sampl$ or screen$)).ti,ab,ot. (29276)
34 (carriage$ or coloniz$ or colonis$).ti,ab,ot. (73157)
35 or/16-34 (1554721)
36 15 and 35 (4035)
37 (enterobacteriaceae infection/pc, dm or exp *Escherichia coli* infection/pc, dm or exp klebsiella infection/pc, dm or proteus infection/pc, dm or serratia infection/pc, dm) and 8 (34)
38 36 or 37 (4042)

MEDLINE (OvidSP): 1946-2013/06/Wk 4
Searched 10 July 2013

1 (ESBL-E or ESBLE).ti,ab,ot. (87)
2 (extend$ adj2 spectrum adj2 (beta or "B") adj2 lactam$ adj3 enterobacter$).ti,ab,ot. (478)
3 or/1-2 (542)
4 (extend$ adj2 spectrum adj2 (beta or "B") adj2 lactam$).ti,ab,ot. (4022)
5 (ESBL or ESBLs).ti,ab,ot. (3350)
6 exp beta-Lactamases/ (17921)
7 or/4-6 (19245)

8 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/ (275429)
9 enterobacteriaceae infections/ or exp *Escherichia coli* infections/ or exp klebsiella infections/ or proteus infections/ or serratia infections/ (39615)
10 (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. (281436)
11 (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. (7040)
12 or/8-11 (373016)
13 7 and 12 (10119)
14 3 or 13 (10120)
15 infection control/ or patient isolation/ or quarantine/ or soaps/ or masks/ or cross infection/pc (40921)
16 hand disinfection/ or antisepsis/ or mandatory testing/ (8283)
17 protective clothing/ or gloves, protective/ (6022)
18 (Infection$ adj2 (control$ or prevention or prophyla$)).ti,ab,ot. (25134)
19 (handwash$ 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$)).ti,ab,ot. (4519)
21 (soap$ 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$).ti,ab,ot. (66700)
22 (alcohol adj3 (gel or gels or wash$ 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$).ti,ab,ot. (62279)
24 (barrier$ adj2 (nurs$ or precaution$)).ti,ab,ot. (702)
25 ((nurs$ or patient$ or inpatient$) adj2 (separat$ or isolat$ or segrat$)).ti,ab,ot. (25035)
26 (cohorted or cohorting or quarantin$ or "cohort nursing").ti,ab,ot. (2873)
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 "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$)).ti,ab,ot. (5322)
28 ((antibiotic$ or anti-biotic$ or antimicrobial$ or anti-microbial$) adj2 (class shift or restrict$ or limit$ or reduc$ or minimi$)).ti,ab,ot. (3414)
29 Mass Screening/ (81740)
30 (screen$ 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$).ti,ab,ot. (910197)
31 ((faeces or feces or faecal$ or fecal$ or rectal$ or rectum or stool or bowel movements$) adj2 (test$ or swab$ or specimen$ or sampl$ or screen$)).ti,ab,ot. (25308)
32 (carriage$ or coloniz$ or colonis$).ti,ab,ot. (64508)
33 or/15-32 (1201380)
34 14 and 33 (3433)
35 (enterobacteriaceae infections/pc, dm or exp *Escherichia coli* infections/pc or exp klebsiella infections/pc or proteus infections/pc or serratia infections/pc) and 7 (120)
36 34 or 35 (3452)

MEDLINE In-Process Citations (OvidSP): up to 2013/07/09
MEDLINE Daily Update (OvidSP): up to 2013/07/09
Searched 10 July 2013

1 (ESBL-E or ESBLE).ti,ab,ot. (20)
2 (extend$ adj2 spectrum adj2 (beta or "B") adj2 lactam$ adj3 enterobacter$).ti,ab,ot. (34)
3 or/1-2 (50)
4 (extend$ adj2 spectrum adj2 (beta or "B") adj2 lactam$).ti,ab,ot. (189)
5 (ESBL or ESBLs).ti,ab,ot. (352)
6 exp beta-Lactamases/ (20)
7 or/4-6 (424)
8 enterobacteriaceae/ or exp citrobacter/ or exp enterobacter/ or exp escherichia/ or exp hafnia/ or exp klebsiella/ or kluyvera/ or exp morganella/ or exp proteus/ or providencia/ or exp serratia/ (241)
9 enterobacteriaceae infections/ or exp *Escherichia coli* infections/ or exp klebsiella infections/ or proteus infections/ or serratia infections/ (49)
10 (enterobacter$ 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. (9982)
11 (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. (375)
12 or/8-11 (10066)
13 7 and 12 (353)
14 3 or 13 (353)
15 infection control/ or patient isolation/ or quarantine/ or soaps/ or masks/ or cross infection/pc (44)
16 hand disinfection/ or antisepsis/ or mandatory testing/ (5)
17 protective clothing/ or gloves, protective/ (8)
18 (Infection$ adj2 (control$ or prevention or prophyla$)).ti,ab,ot. (1642)
19 (handwash$ or handscrub$ or handrub$).ti,ab,ot. (43)

20 ((hand or hands) adj2 (wash$ or clean$ or sanit$ or scrub$ or hygien$ or steril$ or gel or gels or sanitiz$ or sanitis$)).ti,ab,ot. (388)
21 (soap$ 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$).ti,ab,ot. (3864)
22 (alcohol adj3 (gel or gels or wash$ or hand-rub$)).ti,ab,ot. (68)
23 (protective cloth$ or protective$ equipment$ or PPE or glove$ or gown$ or facemask$ or faceshield$ or mask$ or face shield$ or apron$ or face mask$).ti,ab,ot. (5514)
24 (barrier$ adj2 (nurs$ or precaution$)).ti,ab,ot. (47)
25 ((nurs$ or patient$ or inpatient$) adj2 (separat$ or isolat$ or segrat$)).ti,ab,ot. (1031)
26 (cohorted or cohorting or quarantin$ 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$)).ti,ab,ot. (343)
28 ((antibiotic$ or anti-biotic$ or antimicrobial$ or anti-microbial$) adj2 (class shift or restrict$ or limit$ or reduc$ or minimi$)).ti,ab,ot. (268)
29 Mass Screening/ (127)
30 (screen$ 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$).ti,ab,ot. (59752)
31 ((faeces or feces or faecal$ or fecal$ or rectal$ or rectum or stool or bowel movements$) adj2 (test$ or swab$ or specimen$ or sampl$ or screen$)).ti,ab,ot. (1439)
32 (carriage$ or coloniz$ or colonis$).ti,ab,ot. (4404)
33 or/15-32 (75791)
34 14 and 33 (223)
35 (enterobacteriaceae infections/pc, dm or exp *Escherichia coli* infections/pc or exp klebsiella infections/pc or proteus infections/pc or serratia infections/pc) and 7 (0)
36 34 or 35 (223)

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library Issue 6:2013) (Wiley)
Health Technology Assessment Database (HTA) (Cochrane Library Issue 2:2013) (Wiley)
Searched 10 July 2013
http://onlinelibrary.wiley.com/cochranelibrary/search/advanced/shared/searches/12018986898974799530

#1 (ESBL-E or ESBLE) 1
#2 (extend* near/2 spectrum near/2 (beta or "B") near/2 lactam* near/3 enterobacter*) 4
#3 #1 or #2 4
#4 extend* near/2 spectrum near/2 (beta or "B") near/2 lactam* 31
#5 (ESBL or ESBLs) 20
#6 MeSH descriptor: [beta-Lactamases] explode all trees 129
#7 #4 or #5 or #6 155
#8 MeSH descriptor: [Enterobacteriaceae] this term only 157
#9 MeSH descriptor: [Citrobacter] explode all trees 6
#10 MeSH descriptor: [Enterobacter] explode all trees 28
#11 MeSH descriptor: [Enterobacteriaceae Infections] explode all trees 836
#12 MeSH descriptor: [*Escherichia coli* Infections] explode all trees 331
#13 MeSH descriptor: [Klebsiella Infections] explode all trees 68
#14 MeSH descriptor: [Proteus Infections] explode all trees 51
#15 MeSH descriptor: [Serratia Infections] explode all trees 2
#16 MeSH descriptor: [Escherichia] explode all trees 533
#17 MeSH descriptor: [Hafnia] explode all trees 0
#18 MeSH descriptor: [Klebsiella] explode all trees 123
#19 MeSH descriptor: [Kluyvera] explode all trees 0
#20 MeSH descriptor: [Morganella] explode all trees 1
#21 MeSH descriptor: [Proteus] explode all trees 72
#22 MeSH descriptor: [Providencia] explode all trees 2
#23 MeSH descriptor: [Serratia] explode all trees 17
#24 (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
#25 (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
#26 #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 or #23 or #24 or #25 3017
#27 #7 and #26 41
#28 #3 or #27 41

CENTRAL search retrieved 28 results
HTA search retrieved 0 results
INAHTA (International Network of Agencies for Health Technology Assessment): up to 12 July 2013

http://www.inahta.net/Search2/?pub=1
Searched 12 July 2013

Search Term	Results
ESBL	0
ESBLs	0
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	**1**

Appendix 2. Quality assessment criteria

A1. Downs & Black

The following quality assessment criteria developed by Downs & Black [48] 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 healthcare 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%?

A2. Cochrane Collaboration

The following quality assessment criteria developed by the Cochrane Collaboration [49] were used to assess the methodological quality of the two controlled comparative studies included in the analysis section of the report. Each of the studies was assessed individually and graded using the following responses:

- High risk – Corresponding to poor methodological quality
- Low risk – Corresponding to high methodological quality
- Unclear/NR risk – Insufficient information to make a judgement.

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

Domain	Judgement	Criteria	Supporting text
Selection bias			
Random sequence generation	Low risk of bias	The investigators describe a random component in the sequence generation process such as: • Referring to a random number table; • Using a computer random number generator; • Coin tossing; • Shuffling cards or envelopes; • Throwing dice; • Drawing of lots; • Minimization*. * Minimization may be implemented without a random element, and this is considered to be equivalent to being random.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
	High risk of bias	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: • Sequence generated by odd or even date of birth; • Sequence generated by some rule based on date (or day) of admission; • Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example: • Allocation by judgement of the clinician; • Allocation by preference of the participant; • Allocation based on the results of a laboratory test or a series of tests; • Allocation by availability of the intervention.	
	Unclear risk of bias	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'.	
Allocation concealment	Low risk of bias	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: • Central allocation (including telephone, web-based and pharmacy-controlled randomization); • Sequentially numbered drug containers of identical appearance; • Sequentially numbered, opaque, sealed envelopes.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.
	High risk of bias	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: • Using an open random allocation schedule (e.g. a list of random numbers); • Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); • Alternation or rotation; • Date of birth • Case record number • Any other explicitly unconcealed procedure.	
	Unclear risk of bias	Insufficient information to permit judgement of 'Low risk' or 'High risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.	
Performance bias			
Blinding of participants and personnel. Assessments should be made for each main outcome (or class of outcomes).	Low risk of bias	Any one of the following: • No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; • Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.
	High risk of bias	Any one of the following: • No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; • Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.	
	Unclear risk of bias	Any one of the following: • Insufficient information to permit judgement of 'Low risk' or 'High risk'; • The study did not address this outcome.	
Detection bias			
Blinding of outcome assessment Assessments should be made	Low risk of bias	Any one of the following: No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the

Domain	Judgement	Criteria	Supporting text
Selection bias			
for each main outcome (or class of outcomes).	High risk of bias	Any one of the following: • No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; • Blinding of outcome assessment, but likely that the blinding could have been broken and the outcome measurement are likely to be influenced by lack of blinding.	intended blinding was effective.
	Unclear risk of bias	Any one of the following: • Insufficient information to permit judgement of 'Low risk' or 'High risk'; • The study did not address this outcome.	
Attrition bias			
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes).	Low risk of bias	Any one of the following: • No missing outcome data; • Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); • Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; • Missing data have been imputed using appropriate methods.	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.
	High risk of bias	Any one of the following: • Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; • 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; • Potentially inappropriate application of simple imputation.	
	Unclear risk of bias	Any one of the following: • Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided); • The study did not address this outcome.	
Reporting bias			
Selective reporting.	Low risk of bias	Any of the following: • The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; • The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.
	High risk of bias	Any one of the following: • Not all of the study's pre-specified primary outcomes have been reported; • One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; • One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); • One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; • The study report fails to include results for a key outcome that would be expected to have been reported for such a study.	
	Unclear risk of bias	Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category.	
Other bias			
Other sources of bias.	Low risk of bias	The study appears to be free of other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.
	High risk of bias	There is at least one important risk of bias. For example, the study: • Had a potential source of bias related to the specific study design used; or • Has been claimed to have been fraudulent; or • Had some other problem.	
	Unclear risk of bias	There may be a risk of bias, but there is either: • Insufficient information to assess whether an important risk of bias exists; or • Insufficient rationale or evidence that an identified problem will introduce bias.	

Appendix 3. List of studies not meeting inclusion criteria

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 81 studies was excluded (70 studies + 10 duplicates; 1 unobtainable).

A. Excluded studies which do not meet criteria for population/intervention/outcome (70 studies)

1. Suviste J, Gray J, Morgan I, Patel M. Rectal swabs: an increasingly important component of nicu infection surveillance programmes? In: Fourth Congress of the European Academy of Paediatric Societies; 5-9 Sept 2012; Istanbul, Turkey. Arch Dis Child. 2012;97:A334. **Reason for exclusion:** *No relevant data*
2. 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:** *No relevant data*
3. Khun PA, Seng S, Emary K, Moore C, Soeng S, Ngoun C, et al. Surveillance of healthcare-associated infection at Angkor Hospital for Children, Siem Reap, Cambodia. In: Fifteenth International Congress on Infectious Diseases, ICID; 13-16 Jun 2012; Bangkok, Thailand. Int J Infect Dis. 2012;16:e375. **Reason for exclusion:** *No relevant data*
4. 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:** *No relevant data*
5. Gaona C, Rodriguez-Garrido S, Escobar A, Hidalgo R, Garduno E. Molecular and epidemiological analysis of an outbreak of extended-spectrum beta-lactamase-producing Klebsiella pneumoniae using repetitive extragenic palindromicpolymerase chain reaction. In: 22nd European Congress of Clinical Microbiology and Infectious Diseases; 31 May - 3 Apr 2012; London, UK. Clin Microbiol Infect. 2012;18:571-2. **Reason for exclusion:** *No relevant data on transmission*
6. Rodriguez-Bano J. Should all patients harbouring ESBL-producing organisms be isolated? Presented at 22nd European Congress of Clinical Microbiology and Infectious Diseases; 31 May - 3 Apr 2012; London: UK. Clin Microbiol Infect. 2012;18:81. **Reason for exclusion:** *Guidance – no data*
7. 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:** *Results not relevant to ESBL.*
8. Zhuchenko E, Graf K, Vonberg RP. A systematic review of nosocomial outbreaks caused by multidrug-resistant Gram-negative bacteria. Presented at 21st ECCMID/27th ICC; 7-10 May 2011; Milan: Italy. Clin Microbiol Infect. 2011;17:S337-S8. **Reason for exclusion:** *Systematic review (abstract so no ref checking)*
9. Zhuchenko E, Graf K, Vonberg RP. Outbreaks by multi drug resistant Gram negative bacteria - a systematic review. Presented at 63 Jahrestagung der Deutschen Gesellschaft fur Hygiene und Mikrobiologie, DGHM; 25-28 Sept 2011; Essen: Germany. Int J Med Microbiol. 2011;301:33. **Reason for exclusion:** *Systematic review (abstract so no ref checking)*
10. Piso RJ, Grui E, Schibli U, Bulmann M, Bassetti S. Low environmental contamination of rooms in ESBL-positive patients. Presented at 21st ECCMID/27th ICC; 7-10 May 2011; Milan: Italy. Clin Microbiol Infect. 2011;17:S31. **Reason for exclusion**: *Results about screening, not intervention.*
11. Mitra S, Sivakumar P, Oughton J, Ossuetta I. National surveillance study of extended spectrum beta lactamase (ESBL) producing organism infection in neonatal units of England and Wales. Presented at Annual Conference of the Royal College of Paediatrics and Child Health, RCPCH; 4-7 Apr 2011; Warwick: UK. Arch Dis Child. 2011;96:A47. **Reason for exclusion**: Insufficient data
12. Christoph BB, Repa A, Berger A, Pollak A, Haiden N. Contaminated breast milk-source of infection? The transmission of Escherichia coli ESBL to preterm infants through breast milk. Presented at International Congress on Prevention of Congenital Diseases; 13-14 May 2011; Vienna: Austria. J Inherit Metab Dis. 2011;34(Suppl 1). **Reason for exclusion**: Case study- no information on transmission
13. Gavin MA, Master RN, White MJ, Wagner RP, Nelson NA. Surveillance cultures for multi-drug resistant gram negative bacilli from patients admitted from long-term care facilities. Presented at APIC 37th Annual Educational Conference and International Meeting; 11-15 Jul 2010; New Orleans: LA. Am J Infect Control. 2010;38(5):E127-E8. **Reason for exclusion**:No specific results on ESBL
14. Gaind R, Paglietti B, Sehgal R, Rubino S. Outbreak of Proteus mirabilis in neonatal unit - lessons learnt. Presented at 7th International Conference of the Hospital Infection Society; 10-13 Oct 2010; Liverpool: UK. J Hosp Infect. 2010;76:S66. **Reason for exclusion**:No specific transmission results on ESBL
15. Vanneste M, De Waegemaeker P, Bovyn N, Verschraegen G, Claeys G. Isolation of patients with multiresistant Gram-negative rods: a new strategy. Presented at 7th International Conference of the Hospital Infection Society; 10-13 Oct 2010; Liverpool: UK. J Hosp Infect. 2010;76:S57. **Reason for exclusion**: Unclear population (not specific to ESBL)
16. Nieto-Gonzalez M, Del Diego-Salas J, Hernandez-Rodriguez JV, De la Torre-Prados MV, Hidalgo-Gomez F, Ortega M. Nosocomial outbreak due to clonal esbl klebsiella strain at a intensive care unit. Presented at 23rd Annual Congress of the European Society of Intensive Care Medicine, ESICM; 9-13 Oct 2010; Barcelona: Spain. Intensive Care Med. 2010;36:S256. **Reason for exclusion**: No specific transmission results for ESBL

17. Xanthaki A, Kyriakaki A, Paraskeva A, Karaferi A, Skandami V, Balla M, et al. Clinical and environmental sampling of an adult intensive care unit in Greece. Presented at 23rd Annual Congress of the European Society of Intensive Care Medicine, ESICM; 9-13 Oct 2010; Barcelona: Spain. Intensive Care Med. 2010;36:S255. **Reason for exclusion**: Environmental sampling only
18. Rubio-Perez I, Pichiule M, Martin-Perez E, Domingo D, Figuerola A, Larranaga E. Application of infection control measures for multiresistant ESBL-producing bacteria among hospitalized general surgery patients: an institutional study. Presented at 8th World Congress on Trauma, Shock, Inflammation and Sepsis in Conjunction with 23rd SIS-Europe Congress on Surgical Infections and the 2nd Interdisciplinary Summit on Inflammation, TSIS; 9-13 Mar 2010; Munich: Germany. Inflamm Res. 2010;59:s149. **Reason for exclusion**: No specific transmission results for ESBL
19. Candevir A, Kurtaran B, Tasova Y, Gurel D, Inal AS, Kibar F, et al. Nosocomial infection surveillance data of a burn centre, 2005-2009: what we have learnt. Presented at 20th ECCMID; 10-13 Apr 2010; Vienna: Austria. Clin Microbiol Infect. 2010;16:S686. **Reason for exclusion**: Focus on infection rates
20. Lye D, Ng TM, Teng CB, Ling LM, Hsieh IJ, Yeak SC, et al. Computerized surveillance of antibiotic usage and resistance: Monitoring the impact of interventions. Presented at 20th ECCMID; 10-13 Apr 2010; Vienna: Austria. Clin Microbiol Infect. 2010;16:S432. **Reason for exclusion**: No data on ESBL transmission
21. Kramme E, Martin M, Mattner F. Infection control measures taken to control outbreaks with multiresistant Gram negative bacteria. Presented at 61st Conference of the Deutschen Gesellschaft fur Hygiene und Mikrobiologie; 20-23 Sept 2009; Goettingen: Germany. Int J Med Microbiol. 2009;299(Suppl 1):30. **Reason for exclusion**: No data on ESBL transmission
22. Melin S, Toepfer M, Wetterbrandt S, Rensfeldt G, Lofgren S. Molecular typing is a cornerstone for infection control in neonatology: a case with extended-spectrum beta-lactamase Escherichia coli and Staphylococcus aureus. Presented at 19th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); 16-19 May 2009; Helsinki: Finland. Clin Microbiol Infect. 2009;15:S403. **Reason for exclusion**: To specific infection control measures; mainly screening
23. Strenger V, Dosch V, Feierl G, Grisold A, Zarfel G, Resch B, et al., editors. Factors associated with colonisation with extended-spectrum beta-lactamase-producing enterobacteria in newborns hospitalised at the neonatal intensive care unit. Presented at 19th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); 16-19 May 2009; Helsinki: Finland2009. **Reason for exclusion**: No relevan data (risk factors)
24. Brun-Buisson C, Razazi K, Derde LPG, Bonten MJM. Control of colonisation with extended-spectrum beta-lactamase-producing bacteria: reply to Zandstra et al. Intensive Care Med. 2013;39(3):540. **Reason for exclusion**: No relevant data
25. Severin JA, Goessens WH, Vos MC. Response to: Buehlmann et al. 'Effectiveness of a new decolonisation regimen for eradication of extended-spectrum beta-lactamase-producing Enterobacteriaceae'. The Journal of hospital infection. 2012;80(2):182-3; author reply 3-4. **Reason for exclusion**: Wrong population (community)
26. Buehlmann M, Bruderer T, Frei R, Widmer AF. Effectiveness of a new decolonisation regimen for eradication of extended-spectrum -lactamase-producing Enterobacteriaceae. J Hosp Infect. 2011 Feb;77(2):113-7. **Reason for exclusion**:No relevant transmission data
27. Scheithauer S, Oberrohrmann A, Haefner H, Kopp R, Schurholz T, Schwanz T, et al. Compliance with hand hygiene in patients with meticillin-resistant Staphylococcus aureus and extended-spectrum -lactamase-producing enterobacteria. J Hosp Infect. 2010 Dec;76(4):320-3. **Reason for exclusion**:No relevant data
28. Huttner B, Pittet D, Harbarth S. Comment on: Control of extended-spectrum beta-lactamase-producing Klebsiella pneumoniae using a computer-assisted management program to restrict third-generation cephalosporin use. J Antimicrob Chemother. 2008;62(5):1165. **Reason for exclusion**:No relevant data
29. Canut Blasco A. Infections in nursing homes: The most frequent microorganisms, antimicrobial use and bacterial resistance. [Spanish]. Revista Espanola de Geriatria y Gerontologia. 2007;42(SUPPL. 1):27-38. **Reason for exclusion**: No relevant data
30. Moodley P, Coovadia YM, Sturm AW. Intravenous glucose preparation as the source of an outbreak of extended-spectrum beta-lactamase-producing Klebsiella pneumoniae infections in the neonatal unit of a regional hospital in KwaZulu-Natal. S Afr Med J. 2005;95(11 I):861-4. **Reason for exclusion**: No relevant transmission data for ESBL
31. Gavin PJ, Bolden Jr JR, Peterson LR, Thomson Jr RB. Does identification of an extended-spectrum beta-lactamase-producing organism by the microbiology laboratory influence patient management? Infectious Diseases in Clinical Practice. 2006;14(2):81-3. **Reason for exclusion**: No reported transmission results following intervention
32. Inoue M. Hospital outbreak of MEN-1-derived extended spectrum beta-lactamase-producing Klebsiella pneumoniae. Journal of Infection and Chemotherapy. 2001;7(2):124. **Reason for exclusion**: No relevant data
33. Lautenbach E, Fishman NO, Rahal JJ, Urban C, Segal-Maurer S, Horn D. Control of outbreaks due to organisms producing extended-spectrum beta- lactamases [1] (multiple letters). J Am Med Assoc. 1999;281(12):1080-1. **Reason for exclusion**: No relevant data
34. Revathi G, Shannon KP, Stapleton PD, Jain BK, French GL. An outbreak of extended-spectrum, beta-lactamase-producing Salmonella senftenberg in a burns ward. J Hosp Infect. 1998;40(4):295-302. **Reason for exclusion**: No relevant data for ESBL transmission
35. Lowe CF, Kus JV, Salt N, Callery S, Louie L, Khan MA, et al. Nosocomial transmission of New Delhi metallo-b-lactamase-1-producing Klebsiella pneumoniae in Toronto, Canada. Infect Control Hosp Epidemiol. 2013;34(1):49-55. **Reason for exclusion**: No relevant data (risk factors)
36. 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):960-1. **Reason for exclusion**: Wrong population (CPE)
37. 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). **Reason for exclusion**: No relevant data; population unclear

38. 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). **Reason for exclusion**: No relevant data; population unclear
39. Hospenthal DR, Crouch HK, English JF, Leach F, Pool J, Conger NG, et al. Multidrug-resistant bacterial colonization of combat-injured personnel at admission to medical centers after evacuation from Afghanistan and Iraq. Journal of Trauma - Injury, Infection and Critical Care. 2011;71(SUPPL. 1):S52-S7. **Reason for exclusion**:Screening only, no other infection control measures
40. Levy SSS, Mello MJG, Gusmao-filho FAR, Correia JB. Colonisation by extended-spectrum beta-lactamase-producing Klebsiella spp. in a paediatric intensive care unit. J Hosp Infect. 2010;76(1):66-9. **Reason for exclusion**:Screening only, no infection control measures
41. Papadimitriou M, Charachousou E, Hatzaki D, Doudoulakakis A, Parakakis I, Kapetanakis J, et al. Bloodstream infections in a neonatal intensive care unit: a 2-year study. 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):276. **Reason for exclusion**:No detail on intervention reported
42. 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**: No specific intervention or relevant outcomes
43. D'Errico MM, Marigliano A, Pellegrini I, Gioia MG, Savini S, Gigli M, et al. Reporting of a surveillance system of multidrug-resistant organisms in an Italian hospital. Presented at International Conference on Prevention and Infection Control, ICPIC; 29 Jun - 2 Jul 2011; Geneva: Switzerland. BMC Proc. 2011;5(Suppl 6):P298. **Reason for exclusion**: Surveillance; no infection control
44. Le Fournis S, Prouteau C, Kowalczyk F, Joly-Guillou M, Eveillard M. Studying the urinary reservoir of extended-spectrum beta-lactamase-producing Enterobacteriaceae in a teaching hospital. Presented at 21st ECCMID/27th ICC; 7-10 May 2011; Milan: Italy. Clin Microbiol Infect. 2011;17:S143-S4. **Reason for exclusion**: Screening only; no infection control
45. Kunishima H, Chiba J, Hatta M, Nishimaki K, Yamada M, Kitagawa M, et al. ESBL active surveillance culture in patients rehospitalized from other facilities and nursing homes. Presented at 7th International Conference of the Hospital Infection Society; 10-13 Oct 2010; Liverpool: UK. J Hosp Infect. 2010;76:S68. **Reason for exclusion**: Screening only; no infection control
46. Johansson M, Phuong DM, Walther SM, Hanberger H. Need for improved antimicrobial and infection control stewardship in Vietnamese intensive care units. Trop Med Int Health. 2011;16(6):737-43. **Reason for exclusion**: No specific transmission data for ESBL
47. Hoban DJ, Zhanel GG. Introduction to the CANWARD Study (2007-2009). Diagn Microbiol Infect Dis. 2011;69(3):289-90. **Reason for exclusion**: Pathogen resistance study
48. Biran V, Gaudin A, Mariani-Kurdjian P, Doit C, Bingen E, Aujard Y. [Implication of extended-spectrum beta-lactamase enterobacteriaceae in nosocomial infections in neonates]. Arch Pediatr. 2010;17(suppl 4):S150-S3. **Reason for exclusion**: Screening; no infection control
49. Ramphal R. Developing strategies to minimize the impact of extended-spectrum beta-lactamases: focus on cefepime. Clin Infect Dis. 2006;42(SUPPL. 4):S151-S2. **Reason for exclusion**: Comment on management of ESBL
50. Valenti AJ. Towns, gowns, and gloves: the status of infection control in community hospitals. Infect Control Hosp Epidemiol. 2006;27(3):225-7. **Reason for exclusion**: Not specific to ESBL
51. Gupta N, Limbago BM, Patel JB, Kallen AJ. Carbapenem-resistant Enterobacteriaceae: epidemiology and prevention. Clin Infect Dis. 2011 Jul 1;53(1):60-7. **Reason for exclusion**: CPE epidemiology; no ESBL
52. Kim ST, Kim J, Choe Y, Kim YK. The combined anti-apoptotic effect from Tamiflu and pinoresinol of Forsythia fructus extract against influenza virus infection. Korean Journal of Pharmacognosy. 2011;42(1):9-14. **Reason for exclusion**: No relevant data
53. Kamath S, Mallaya S, Shenoy S. Nosocomial infections in neonatal intensive care units: Profile, risk factor assessment and antibiogram. Indian J Pediatr. 2010;77(1):37-9. **Reason for exclusion**:No relevant data
54. Carmeli Y, Akova M, Cornaglia G, Daikos GL, Garau J, Harbarth S, et al. Controlling the spread of carbapenemase-producing Gram-negatives: therapeutic approach and infection control. Clin Microbiol Infect. 2010 Feb;16(2):102-11. **Reason for exclusion**: CPE population(wrong population) and guidance document
55. Ivanova D, Markovska R, Hadjieva N, Schneider I, Mitov I, Bauernfeind A. Extended-spectrum beta-lactamase-producing Serratia marcescens outbreak in a Bulgarian hospital. J Hosp Infect. 2008 Sep;70(1):60-5. **Reason for exclusion**:Unclear infection control measures; no relevant transmission data
56. Bissett L. ESBL-producing Enterobacteriaceae: controlling the spread of infection. Br J Nurs. 2007 Jun 14-27;16(11):644-7. **Reason for exclusion**:Guidance/background paper
57. Ben-Ami R, Schwaber MJ, Navon-Venezia S, Schwartz D, Giladi M, Chmelnitsky I, et al. Influx of extended-spectrum beta-lactamase-producing enterobacteriaceae into the hospital. Clin Infect Dis. 2006 Apr 1;42(7):925-34. **Reason for exclusion**: Screening study; data not linked to infection control interventions
58. Velasco E, Byington R, Martins CSA, Schirmer M, Dias LCM, Goncalves VMSC. Bloodstream infection surveillance in a cancer centre: a prospective look at clinical microbiology aspects. Clin Microbiol Infect. 2004 Jun;10(6):542-9. **Reason for exclusion**: Screening, no infection control
59. Muller M, McGeer A. Variation in approach to ESBL Enterobacteriaceae among infection control practitioners: results of an Ontario-wide survey. Can Commun Dis Rep. 2002 Aug 1;28(15):121-4. **Reason for exclusion**: Survey of infection control practices.
60. Petros AJ, O'Connell M, Roberts C, Wade P, van Saene HK. Systemic antibiotics fail to clear multidrug-resistant Klebsiella from a pediatric ICU. Chest. 2001 Mar;119(3):862-6. **Reason for exclusion**: Screening, no infection control

61. Moustaoui N, Bensghir R, Mjahed K, Hakim K, Aimhand R, Boudouma M, et al. Digestive tract colonization with extended spectrum betalactamase producing Enterobacteriaceae in a surgical intensive care unit in Casablanca. J Hosp Infect. 2000 Nov;46(3):238-40. **Reason for exclusion**: Screening, no infection control.

62. Asensio A, Oliver A, Gonzalez-Diego P, Baquero F, Perez-Diaz JC, Ros P, et al. Outbreak of a multiresistant Klebsiella pneumoniae strain in an intensive care unit: antibiotic use as risk factor for colonization and infection. Clin Infect Dis. 2000 Jan;30(1):55-60. **Reason for exclusion**: Not specific to ESBL

63. Kim JY, Kim MJ. Control of extended-spectrum beta-lactamase-producing Klebsiella pneumoniae by utilizing a computer-assisted management program to restrict third-generation cephalosporin use - Authors' response. J Antimicrob Chemother. 2008;62(5):1165-6. **Reason for exclusion**: Intervention not relevant

64. Adjide CC, Biendo M, Rousseau F, Hamdad-Daoudi F, Thomas D, Laurans G, et al. [Extended-spectrum betalactamases producing Escherichia coli: a new health-care associated infection threat?]. Pathol Biol (Paris). 2006 Oct-Nov;54(8-9):510-7. **Reason for exclusion**: Intervention unclear

65. Martins IS, Moreira BM, Riley LW, Santoro-Lopes G. Outbreak of extended-spectrum beta-lactamase-producing Klebsiella pneumoniae infection among renal transplant recipients. J Hosp Infect. 2006;64(3):305-8. **Reason for exclusion**:Data related to antibioti use rather than infection control measures

66. 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**: No relevant data

67. Espinosa de los Monteros LE, Silva-Sanchez J, Jimenez LV, Rojas T, Garza-Ramos U, Valverde V. Outbreak of infection by extended-spectrum beta-lactamase SHV-5-producing Serratia marcescens in a Mexican hospital. J Chemother. 2008 Oct;20(5):586-92. **Reason for exclusion**: Relates to screening, not infection control

68. Krawczyk B, Samet A, Czarniak E, Szczapa J, Kur J. Extended-spectrum beta-lactamase-producing Klebsiella pneumoniae in a neonatal unit: control of an outbreak using a new ADSRRS technique. Polish Journal of Microbiology/Polskie Towarzystwo Mikrobiologow/The Polish Society of Microbiologists. 2005;54(2):105-10. **Reason for exclusion**: Results data unclear; no specific data on transmission

69. Burak S, Engelhart S, Exner M, Marklein G, Purr I, Putensen C, et al. [Nosocomial outbreaks with Klebsiella pneumoniae strains in intensive care units]. Chemotherapie Journal. 2006;15(4):112-8. **Reason for exclusion**: Results realted to screening and no data on infection control measures

70. Goddard S, Muller MP. The efficacy of infection control interventions in reducing the incidence of extended-spectrum -lactamase-producing Enterobacteriaceae in the nonoutbreak setting: A systematic review. Am J Infect Control. 2011 Sep;39(7):599-601. **Reason for exclusion**: Systematic review and not an individual study.

B. Excluded: duplicate studies (ten studies)

71. Knudsen J, Andersen SE. A significant impact on the rate of ESBL-producing Klebsiella pneumoniae by changing the antibiotic policy and consumption. Presented at 21st ECCMID/27th ICC; 7 - 10 May 2011; Milan: Italy. Clin Microbiol Infect. 2011;17:S271.

72. Bragesjo F, Hallberg M. Back to basics: Governing antibacterial resistance by means of mundane technoscience and accountability relations in a context of risk. Health, Risk and Society. 2011;13(7-8):691-709.

73. Tamma PD, Savard P, Pal T, Sonnevend A, Perl TM, Milstone AM. An outbreak of extended-spectrum beta-lactamase-producing Klebsiella pneumoniae in a neonatal intensive care unit. Infect Control Hosp Epidemiol. 2012;33(6):631-4.

74. Biran V, Gaudin A, Mariani-Kurdjian P, Doit C, Bingen E, Aujard Y. [Implication of extended-spectrum beta-lactamase enterobacteriaceae in nosocomial infections in neonates]. Arch Pediatr. 2010;17(suppl 4):S150-S3.

75. Levy SSS, Mello MJG, Gusmao-filho FAR, Correia JB. Colonisation by extended-spectrum beta-lactamase-producing Klebsiella spp. in a paediatric intensive care unit. J Hosp Infect. 2010;76(1):66-9.

76. Eveillard M, Biendo M, Canarelli B, Daoudi F, Laurans G, Rousseau F, et al. [Spread of Enterobacteriaceae producing broad-spectrum beta-lactamase and the development of their incidence over a 16-month period in a university hospital center]. Pathol Biol (Paris). 2001 Sep;49(7):515-21.

77. Lowe CF, Katz K, McGeer AJ, Muller MP. Efficacy of admission screening for extended-spectrum beta-lactamase producing Enterobacteriaceae. PLoS One. 2013;8(4).

78. Prospero E, Barbadoro P, Esposto E, Manso E, Martini E, Savini S, et al. Extended-spectrum beta-lactamases Klebsiella pneumoniae: multimodal infection control program in intensive care units. J Prev Med Hyg. 2010 Sep;51(3):110-5.

79. Severin JA, Goessens WH, Vos MC. Response to: Buehlmann et al. 'Effectiveness of a new decolonisation regimen for eradication of extended-spectrum beta-lactamase-producing Enterobacteriaceae'. The Journal of hospital infection. 2012;80(2):182-3; author reply 3-4.

80. Moodley P, Coovadia YM, Sturm AW. Intravenous glucose preparation as the source of an outbreak of extended-spectrum beta-lactamase-producing Klebsiella pneumoniae infections in the neonatal unit of a regional hospital in KwaZulu-Natal. S Afr Med J. 2005;95(11 I):861-4.

C. Excluded: unobtainable study

81. 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

The following studies met the inclusion criteria and provided sufficient information to meet the ORION statement [1] 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)**
Barbut 2013	Barbut F, Yezli S, Mimoun M, Pham J, Chaouat M, Otter JA. Reducing the spread of Acinetobacter baumannii and methicillin-resistant Staphylococcus aureus on a burns unit through the intervention of an infection control bundle. Burns 2013;39 (3):395-403.
Contero 2007	Conterno LO, Shymanski J, Ramotar K, Toye B, Zvonar R, Roth V. Impact and cost of infection control measures to reduce nosocomial transmission of extended-spectrum β-lactamase-producing organisms in a non-outbreak setting. J Hosp Infect 2007;65 (4):354-360
Johnson 2005	Johnson PDR, Martin R, Burrell LJ, Grabsch EA, Kirsa SW, O'Keeffe J, et al. Efficacy of an alcohol/chlorhexidine hand hygiene program in a hospital with high rates of nosocomial methicillin-resistant Staphylococcus aureus (MRSA) infection. Med J Aust 2005;183 (10):509-14.
Laurent 2008	Laurent C, Rodriguez-Villalobos H, Rost F, Strale H, Vincent JL, Deplano A, et al. Intensive care unit outbreak of extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* controlled by cohorting patients and reinforcing infection control measures. Infection Control & Hospital Epidemiology 2008;29 (6):517-24.
Lee 2007	Lee J, Pai H, Kim YK, Kim NH, Eun BW, Kang HJ, et al. Control of extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in a children's hospital by changing antimicrobial agent usage policy. J Antimicrob Chemother 2007;60 (3):629-37.
Lucet 1999	Lucet JC, Decre D, Fichelle A, Joly-Guillou ML, Pernet M, Deblangy C, et al. Control of a prolonged outbreak of extended-spectrum beta-lactamase-producing enterobacteriaceae in a university hospital. Clin Infect Dis 1999;29 (6):1411-8.
Prospero 2010	Prospero E, Barbadoro P, Esposto E, Manso E, Martini E, Savini S, et al. Extended-spectrum beta-lactamases *Klebsiella pneumoniae*: multimodal infection control program in intensive care units. Journal of Preventive Medicine & Hygiene 2010;51 (3):110-5
Souweine 2000	Souweine B, Traore O, Aublet-Cuvelier B, Bret L, Sirot J, Laveran H, et al. Role of infection control measures in limiting morbidity associated with multi-resistant organisms in critically ill patients. J Hosp Infect 2000;45 (2):107-16.
Trick 2004	Trick WE, Weinstein RA, DeMarais PL, Tomaska W, Nathan C, McAllister SK, et al. Comparison of routine glove use and contact-isolation precautions to prevent transmission of multidrug-resistant bacteria in a long-term care facility. J Am Geriatr Soc 2004;52 (12):2003-9.
Wen 2010	Wen Z, Wei X, Xue F, Hao F, Zhu Y, Ma N, et al. Intervention study of the association of antibiotic utilization measures with control of extended-spectrum beta-lactamase (ESBL)-producing bacteria. Microbes and Infection 2010;12 (10):710-715.

** Study ID used throughout the review*

B. Studies meeting the inclusion criteria but not included in the review analyses; with reasons for exclusion (ORION criteria) (87 studies)

The following studies met the inclusion criteria and but did not provide sufficient information to meet the ORION statement [1] for criteria 9 (intervention reporting) and 17 (outcome reporting and estimation). These studies are 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)**
Abecasis 2011	Abecasis F, Sarginson RE, Kerr S, Taylor N, Van Saene HKF. Is selective digestive decontamination useful in controlling aerobic Gram-negative bacilli producing extended spectrum beta-lactamases? Microb Drug Resist 2011;17 (1):17-23.
Ahren 2010	Ahren C, Andersson M, Forsell M, Helldahl L, Karami N, Larsson L, et al. Investigation and control of an outbreak with CTX-M-15-producing E. coli of sequence types 131 and 1441 in a neonatal surgical ward. In: Journal of Hospital Infection. Conference: 7th International Conference of the Hospital Infection Society Liverpool United Kingdom. Conference Start: 20101010 Conference End: 20101013. Conference Publication: (var.pagings). 76 (pp S62), 2010. Date of Publication: October 2010., 2010.
Ajao 2013	Ajao AO, Johnson JK, Harris AD, Zhan M, McGregor JC, Thom KA, et al. Risk of acquiring extended-spectrum -lactamase-producing *Klebsiella* species and *Escherichia coli* from prior room occupants in the intensive care unit. Infection Control & Hospital Epidemiology 2013;34 (5):453-8.

Study ID*	Bibliographic details of publication (s)**
Al Sweih 2011	Al Sweih N, Salama MF, Jamal W, Al Hashem G, Rotimi VO. An outbreak of CTX-M-15-producing *Klebsiella pneumoniae* isolates in an intensive care unit of a teaching hospital in Kuwait. Indian Journal of Medical Microbiology 2011;29 (2):130-5.
Alsterlund 2009	[Alsterlund R, Carlsson B, Gezelius L, Haeggman S, Olsson-Liljequist B. Multiresistant CTX-M-15 ESBL-producing *Escherichia coli* in southern Sweden: Description of an outbreak. Scand J Infect Dis 2009;41 (6-7):410-5.
Alverez-Lerma 2002	Alvarez-Lerma F, Gasulla Guillermo M, Abad Peruga V, Pueyo Pont MJ, Tarrago Eixarch E. [Effectiveness of contact isolation in the control of multiresistant bacteria in an intensive care service]. Enferm Infecc Microbiol Clin 2002;20 (2):57-63.
Andersson 2012	Andersson H, Lindholm C, Iversen A, Giske CG, Ortqvist A, Kalin M, et al. Prevalence of antibiotic-resistant bacteria in residents of nursing homes in a Swedish municipality: healthcare staff knowledge of and adherence to principles of basic infection prevention. [Erratum appears in Scand J Infect Dis. 2012 Sep;44 (9):649]. Scand J Infect Dis 2012;44 (9):641-9.
Aumeran 2010	Aumeran C, Poincloux L, Souweine B, Robin F, Laurichesse H, Baud O, et al. Multidrug-resistant *Klebsiella pneumoniae* outbreak after endoscopic retrograde cholangiopancreatography. Endoscopy 2010;42 (11):895-9.
Barbut 1994	Barbut F, Soulier A, Ollivier JM, Blons H, Lienhart A, Petit JC. Prevention of transmission of extended-spectrum beta-lactamases Enterobacteriaceae (ESBLE) in surgical ICU by nursing reorganization. [French]. Medecine et Maladies Infectieuses 1994;24 (SPEC. ISS. JUNE):698-704. Soulier A, Barbut F, Ollivier JM, Petit JC, Lienhart A. Decreased transmission of Enterobacteriaceae with extended-spectrum beta-lactamases in an intensive care unit by nursing reorganization. J Hosp Infect 1995;31 (2):89-97.
Betsch 2010	Betsch BY, Droz S, Bogli-Stuber K, Muhlemann K. Transmission rate of ESBL-producing Enterobacteriaceae within the hospital and in households. In: Clinical Microbiology and Infection. Conference: 20th ECCMID Vienna Austria. Conference Start: 20100410 Conference End: 20100413. Conference Publication: (var.pagings). 16 (pp S371), 2010. Date of Publication: April 2010., 2010.
Boszczowski 2005	Boszczowski I, Nicoletti C, Puccini DMT, Pinheiro M, Soares RE, Van der Heijden IM, et al. Outbreak of extended spectrum beta-lactamase-producing *Klebsiella pneumoniae* infection in a neonatal intensive care unit related to onychomycosis in a health care worker. Pediatr Infect Dis J 2005;24 (7):648-50.
Bragesjo 2011	Bragesjo F, Hallberg M. Back to basics: Governing antibacterial resistance by means of mundane technoscience and accountability relations in a context of risk. Health, Risk and Society 2011;13 (7-8):691-709.
Calbo 2009	[Calbo E, Riera M, Freixas N, Nicolas C, Monistrol O, Xercavins M, et al. Food-borne nosocomial outbreak due to ESBL-producing *Klebsiella pneumoniae* (SHV-38). Epidemiology and successful control. In: Clinical Microbiology and Infection. Conference: 19th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) Helsinki Finland. Conference Start: 20090516 Conference End: 20090519. Conference Publication: (var.pagings). 15 (pp S216), 2009. Date of Publication: May 2009., 2009. Calbo E, Freixas N, Xercavins M, Riera M, Nicolas C, Monistrol O, et al. Foodborne nosocomial outbreak of SHV1 and CTX-M-15-producing *Klebsiella pneumoniae*: epidemiology and control. Clin Infect Dis 2011;52 (6):743-9.
Carbonne 2002	[Carbonne A, Albertini MT, Astagneau P, Benoit C, Berardi L, Berrouane Y, et al. Surveillance of methicillin-resistant Staphylococcus aureus (MRSA) and Enterobacteriaceae producing extended-spectrum beta-lactamase (ESBLE) in Northern France: A five-year multicentre incidence study. J Hosp Infect 2002;52 (2):107-113.
Carpentier 2012	[Carpentier M, Appere V, Saliou P, de Tinteniac A, Floch H, Le Gall F, et al. Outbreak of extended spectrum beta-lactamase-producing *Klebsiella pneumoniae* in an intensive care unit (Brest). Medecine et Maladies Infectieuses 2012;42 (10):501-9.
Cassettari 2006	Cassettari VC, Silveira IRd, Balsamo AC, Franco F. Outbreak of extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* in an intermediate-risk neonatal unit linked to onychomycosis in a healthcare worker. J Pediatr (Rio J) 2006;82 (4):313-6.
Cheng 2009	Cheng VCC, Tai JWM, Chan WM, Lau EHY, Chan JFW, To KKW, et al. Sequential introduction of single room isolation and hand hygiene campaign in the control of methicillin-resistant Staphylococcus aureus in intensive care unit. BMC Infectious Diseases 2009;10 (263).
Christiaens 2008	Christiaens G, Barbier C, Warnotte J, Mutsers J. Implementation of an infection control programme to limit the spread of extended-spectrum beta-lactamase-producing Enterobacteriaceae in a Belgian university hospital. J Hosp Infect 2008;68 (4):366-7.
Coovadia 1992	Coovadia YM, Johnson AP, Bhana RH, Hutchinson GR, George RC, Hafferjee IE. Multiresistant *Klebsiella pneumoniae* in a neonatal nursery: The importance of maintenance of infection control policies and procedures in the prevention of outbreaks. J Hosp Infect 1992;22 (3):197-205.
Cukier 1999	[Cukier L, Lutzler P, Bizien A, Avril JL. [Investigation of an epidemic of an extended spectrum beta-lactamase producing *Escherichia coli* in a geriatrics department]. Pathol Biol 1999;47 (5):440-4. Cukier L, Avril JL, Lutzler P, Bizien A. Interest of ribotyping during an outbreak of nosocomial urinary tract infections of multiresistant *Escherichia coli*. [French]. Revue de Geriatrie 2003;28 (8):637-644.
David 2006	David MD, Weller TMA, Lambert P, Fraise AP. An outbreak of Serratia marcescens on the neonatal unit: a tale of two clones. J Hosp Infect 2006;63 (1):27-33.

Study ID*	Bibliographic details of publication (s)**
de Celles 2013	Domenech de Celles M, Zahar JR, Abadie V, Guillemot D. Limits of patient isolation measures to control extended-spectrum beta-lactamase-producing Enterobacteriaceae: model-based analysis of clinical data in a pediatric ward. BMC Infectious Diseases 2013;13 (1).
De-Jong 2012	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. In: Clinical Microbiology and Infection. Conference: 22nd European Congress of Clinical Microbiology and Infectious Diseases London United Kingdom. Conference Start: 20120331 Conference End: 20120403. Conference Publication: (var.pagings). 18 (pp 14), 2012. Date of Publication: April 2012., 2012.
Demir 2008	Demir S, Soysal A, Bakir M, Kaufmann ME, Yagci A. Extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* in paediatric wards: A nested case-control study. J Paediatr Child Health 2008;44 (10):548-553.
Derde 2011	Derde LP, Dautzenberg MJ, Van Duijn PJ, Brun-Buisson C, Bonten MJ. Colonisation and transmission of resistant bacteria in 13 European intensive care units. In: Clinical Microbiology and Infection. Conference: 21st ECCMID/27th ICC Milan Italy. Conference Start: 20110507 Conference End: 20110510. Conference Publication: (var.pagings). 17 (pp S58), 2011. Date of Publication: May 2011., 2011.
Doudoulakakis 2011	Doudoulakakis A, Nika A, Giakkoupi P, Papadimitriou M, Papaioannou A, Kapetanakis J, et al. Outbreak of Enterobacter cloacae ESBL (+) colonisation in a neonatal intensive care unit in Greece. In: Clinical Microbiology and Infection. Conference: 21st ECCMID/27th ICC Milan Italy. Conference Start: 20110507 Conference End: 20110510. Conference Publication: (var.pagings). 17 (pp S716-S717), 2011. Date of Publication: May 2011., 2011.
Eveillard 2001	Eveillard M, Biendo M, Canarelli B, Daoudi F, Laurans G, Rousseau F, et al. Diffusion of enterobacteriaceae producing extended-spectrum beta-lactamase and evolution of their incidence during a 16-month period in a teaching hospital. [French]. Pathol Biol 2001;49 (7):515-521. Eveillard M, Eb F, Tramier B, Schmit JL, Lescure FX, Biendo M, et al. Evaluation of the contribution of isolation precautions in prevention and control of multi-resistant bacteria in a teaching hospital. J Hosp Infect 2001;47 (2):116-24.
Fankhauser 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.
French 1996	French GL, Shannon KP, Simmons N. Hospital outbreak of *Klebsiella pneumoniae* resistant to broad-spectrum cephalosporins and beta-lactam-beta-lactamase inhibitor combinations by hyperproduction of SHV-5 beta-lactamase. J Clin Microbiol 1996;34 (2):358-63.
Giuffre 2013	Giuffre M, Cipolla D, Bonura C, Geraci DM, Aleo A, Di Noto S, et al. Outbreak of colonizations by extended-spectrum beta-lactamase-producing *Escherichia coli* sequence type 131 in a neonatal intensive care unit, Italy. Antimicrobial Resistance and Infection Control 2013;2 (1).
Gonzalez2011	Gonzalez R AC, Gil G F, Solorzano R M, Cruz G J, Puig P J, Suarez S M, et al. [Outbreak of multiresistant and extended spectrum -lactamase producing *Klebsiella pneumoniae* in a high risk neonatal unit]. Revista Chilena de Infectologia 2011;28 (1):28-34.
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.
Grogan 1998	Grogan J, Murphy H, Butler K. Extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* in a Dublin paediatric hospital. Br J Biomed Sci 1998;55 (2):111-7.
Hammami 1991	Hammami A, Arlet G, Ben Redjeb S, Grimont F, Ben Hassen A, Rekik A, et al. Nosocomial outbreak of acute gastroenteritis in a neonatal intensive care unit in Tunisia caused by multiply drug resistant Salmonella wien producing SHV-2 beta-lactamase. European Journal of Clinical Microbiology & Infectious Diseases 1991;10 (8):641-6.
Hanberger 2009	Hanberger H, Arman D, Gill H, Jindrak V, Kalenic S, Kurcz A, et al. Surveillance of microbial resistance in European Intensive Care Units: A first report from the Care-ICU programme for improved infection control. Intensive Care Med 2009;35 (1):91-100.
Harris 2007	Harris AD, Kotetishvili M, Shurland S, Johnson JA, Morris JG, Nemoy LL, et al. How important is patient-to-patient transmission in extended-spectrum beta-lactamase *Escherichia coli* acquisition. Am J Infect Control 2007;35 (2):97-101.
Herrmann 2009	Herrmann J, Cloppenburg E, Roth C, Pfeifer Y. Neonatal intensive care unit outbreak of extended-spectrum beta-lactamase-produdng *Escherichia coli* controlled by treatment with probiotics. In: International Journal of Medical Microbiology. Conference: 61st Conference of the Deutschen Gesellschaft fur Hygiene und Mikrobiologie. Conference Publication: (var.pagings). 299 (pp 28), 2009. Date of Publication: September 2009., 2009.
Hilty 2012	Hilty M, Betsch BY, Bogli-Stuber K, Heiniger N, Stadler M, Kuffer M, et al. Transmission dynamics of extended-spectrum -lactamase-producing enterobacteriaceae in the tertiary care hospital and the household setting. Clin Infect Dis 2012;55 (7):967-975.
Hobson 1996	Hobson RP, MacKenzie FM, Gould IM. An outbreak of multiply-resistant *Klebsiella pneumoniae* in the Grampian region of Scotland. J Hosp Infect 1996;33 (4):249-62.
Hollander 2001	Hollander R, Ebke M, Barck H, von Pritzbuer E. Asymptomatic carriage of *Klebsiella pneumoniae* producing extended-spectrum beta-lactamase by patients in a neurological early rehabilitation unit: management of an outbreak. J Hosp Infect 2001;48 (3):207-13.

Study ID*	Bibliographic details of publication (s)**
Inan 2012	Inan A, Ozgultekin A, Akcay SS, Engin DO, Turan G, Ceran N, et al. Alterations in bacterial spectrum and increasing resistance rates in isolated microorganisms from device-associated infections in an intensive care unit of a teaching hospital in Istanbul (2004-2010). Japanese Journal of Infectious Diseases 2012;65 (2):146-151.
Jansens 2010	Jansens H, Goovaerts E, Van Laer F. Evaluation of the implementation of a change in isolation precautions for extended-spectrum beta-lactamase producing Enterobacteriaceae (ESBL-E). In: Journal of Hospital Infection. Conference: 7th International Conference of the Hospital Infection Society Liverpool United Kingdom. Conference Start: 20101010 Conference End: 20101013. Conference Publication: (var.pagings). 76 (pp S56), 2010. Date of Publication: October 2010., 2010.
Kassis-Chikhani 2004	Kassis-Chikhani N, Vimont S, Asselat K, Trivalle C, Minassian B, Sengelin C, et al. CTX-M beta-lactamase-producing *Escherichia coli* in long-term care facilities, France. Emerg Infect Dis 2004;10 (9):1697-8.
Knudsen 2011	Knudsen J, Andersen SE. A significant impact on the rate of ESBL-producing *Klebsiella pneumoniae* by changing the antibiotic policy and consumption. In: Clinical Microbiology and Infection. Conference: 21st ECCMID/27th ICC Milan Italy. Conference Start: 20110507 Conference End: 20110510. Conference Publication: (var.pagings). 17 (pp S271), 2011. Date of Publication: May 2011., 2011.
Kola 2007	Kola A, Holst M, Chaberny IF, Ziesing S, Suerbaum S, Gastmeier P. Surveillance of extended-spectrum beta-lactamase-producing bacteria and routine use of contact isolation: experience from a three-year period. J Hosp Infect 2007;66 (1):46-51.
Komatsu 2001	Komatsu M, Ikeda N, Aihara M, Nakamachi Y, Kinoshita S, Yamasaki K, et al. Hospital outbreak of MEN-1-derived extended spectrum beta-lactamase-producing *Klebsiella pneumoniae*. J Infect Chemother 2001;7 (2):94-101.
Kruse 2010	Kruse EB, Conrad A, Wenzler-Rottele S, Jonas D, Dettenkofer M, Wolkewitz M, et al. Extended-spectrum beta-lactamase-producing Enterobacter cloacae in mobile dialysis units in the medical and surgical departments of a university hospital: a case-control study. J Hosp Infect 2010;75 (1):33-6.
Laffer 2009	Laffer R, Michot M, Buehlmann M, Mohr C, Bregenzer T, Fankhauser H. Nosocomial outbreak of an extended-spectrum beta-lactamase producing *Klebsiella pneumoniae* strain on a medical intensive care unit. In: Clinical Microbiology and Infection. Conference: 19th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) Helsinki Finland. Conference Start: 20090516 Conference End: 20090519. Conference Publication: (var.pagings). 15 (pp S215), 2009. Date of Publication: May 2009., 2009.
Landelle 2010	Landelle C, Lesprit P, Legrand P, Cizeau F, Soing-Altrach S, Brun-Buisson C, et al. Extended nosocomial outbreak with multidrug-resistant acinetobacter baumannii in a French university hospital. In: Clinical Microbiology and Infection. Conference: 20th ECCMID Vienna Austria. Conference Start: 20100410 Conference End: 20100413. Conference Publication: (var.pagings). 16 (pp S365-S366), 2010. Date of Publication: April 2010., 2010.
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** Study ID used throughout the review*

*** Main publication is 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.*