Supplementary data

Appendix 1 – Glossary

AmpC β-lactamases: clinically important cephalosporinases encoded by the chromosomes of many Enterobacteriaceae or (less often) by plasmids. High-level expression confers resistance to penicillins (except temocillin), cephalosporins (except cefepime), aztreonam and penicillin- β-lactamase inhibitor combinations.

Antimicrobial: A substance that kills or inhibits the growth of microorganisms. This includes antibiotics and totally synthetic compounds.

Bacteraemia: The presence of micro-organisms in the blood stream

β-lactamases: Enzymes produced by some bacteria that confer resistance to β-lactam antibiotics such as penicillins and cephalosporins, by breaking down the central structure of the antibiotic.

Carbapenemases: These are β-lactamases that inactivate carbapenems such as meropenem; most also attack and confer resistance to penicillins and cephalosporins

CBA – (Controlled before and after study) is a more limited assessment than interrupted time series because it does not contain an initial pre-study period to examine underlying trends not a post-study period to assess the sustainability of trend, A cross-over study design may exclude bias due to sequential change,

CCG: Clinical Commissioning Group. This is a locality based authority in England responsible for primary care services and placing financial contracts with local hospitals for specific services

CQUIN: NHS England Commissioning for Quality and Innovation payments framework, to encourage care providers to share and continually improve how care is delivered and to achieve transparency and overall improvement in healthcare.

Cluster randomized controlled clinical trial. This is a trial where groups of individuals rather than individuals are randomized to treatment. This complex study design may reduce the chances of one patient's treatment having an effect on detection of effects in a patient randomized to a different treatment in the dame environment.

Colonization: Situation whereby microorganisms establish themselves in a particular environment, such as a body surface, without producing disease

Community-acquired: infection that is acquired outside of hospitals.

Community-onset or community-associated: usually defined as infection or colonization detected in an outpatient or within 48 hours of hospital admission. Recommended to permit extension to 72hours

CCT – (Controlled clinical trial) A ckinical trial where there is a comparative arm that is not randomized.

ESBL (extended-spectrum β-lactamase): β-Lactamases that attack cephalosporins with an oxyimino side chain, for example, cefotaxime, ceftriaxone, ceftazidime, ceftolozane as well as the oxyimino-monobactam aztreonam. Unlike AmpC β-lactamases (q.v.) they are inhibited by clavulanic acid and tazobactam and unlike carbapenemases (q.v.) they do not attack carbapenems. Avibactam inhibitis them and AmpC β-lactamases.

Healthcare – associated (acquired) : infection or colonization detected in an in-patient more than 48 hours after hospital admission or in a resident of a nursing (or residential) home.Recommended to permit extension to 72hours

Hospital-onset or Hospital–associated (-acquired): infection or colonization detected in an inpatient more than 48 hours after hospital admission. Recommended to permit extension to 72 hours.

IMP carbapenemase (of MBL class) prevalent particularly in Asia and Australia sometimes in association with a second carbapenemase (*bla*$_{KPC)}$ gene

Infection: Invasion by and multiplication of pathogenic microorganisms in the body, producing tissue injury and disease, requiring treatment.

ITS – (Interrupted time series). A series of sequential cases where an intervention is made in the middle of the study as in before and after studies but additional time periods before and after the two comparative periods are included to give information omn prior trends and sustainability. studied. There may be further interventions in the series similarly studied.

KPC *Klebsiella pneumoniae* carbapenemase-producing bacteria are drug-resistant Gram negative bacilli which spread rapidly and cause significant morbidity and mortality. They are the most prevalent carbapenemase producers encoded by the *bla*$_{KPC}$ gene, which can be found in other Gram negative species.

MBL (Metallo β-lactamase) producing Gram negative bacteria use a Zn^{2+} ion in expressing resistance to carbapenems and other B-lactams

MDR GNB – (Multi-drug resistant Gram-negative bacteria) are defined as bacteria resistant to at least three different antibiotic classes or susceptible to only one or two classes.

NDM New Delhi metallo β-lactamase is a carbapenemase located on a mobile genetic element *bla*$_{\text{NDM-1}}$ and is found on plasmids of various sizes. It is found in various species making outbreaks more difficult to identify.

OXA-48 carbapenemases hydrolyze penicillins at a high level but carbapenems at a low level sparing broad spectrum cephalosporins and are no susceptible to β-lactamase inhibitors. Recogniition in the laboratory can be difficult. The gene *bla*$_{\text{OXA-48}}$ is carried on a transposon and can be in a plasmid or chromosome.

Outbreak: at least two similar (i.e. not distinct) cases related in time and place

Porins: These are proteins that span the outer membrane of Gram-negative bacteria and mycobacteria forming pores that allow the entry of small water-soluble molecules, including antibiotics.

RCT (randomised controlled trial). Trials where patient allocation to the control and test arms of the study are allocated at random. They can be open label where treating physicians know which arm a patient has been allocated to or blinded where this is not the case. The latter is less likely to be subject to bias.

VIM MBL is a carbapenemase predominantly found in *Pseudomonas aeruginosa* but found in Enterobacteriaceae as well. The genes *bla*$_{\text{VIM}}$ are located on mobile integrons .

Appendix 2 Remit scope and related NICE guidelines

Joint BSAC/HIS/BIA Working Party on Multi-resistant Gram-negative bacteria

2.1. Guideline title

Treatment of MDR Gram-negative bacteria – report from a Joint Working Party

Short title: Treatment of Multi-Drug-Resistant Gram negative bacteria

2.2. Clinical need for the guideline

Epidemiology

There are a rising number of MDR Gram-negative infections across community and hospital care and the dual problems of finding an appropriate antibiotic and preventing spread.

APRHAI has recently produced brief guidelines on infection control and treatment options for these infections.

There is significant interest attracted by the May 2010 BSAC conference examining the dearth of new antibiotics effective against Gram-negative bacteria.

The Department of Health's recognised that whilst control of MRSA and C difficile has been relatively successful, Gram-negative infections have continued to increase.

Consequent to this is the surveillance subcommittee of APRHAI recommendation that E. coli bacteraemia be included in mandatory surveillance.

Current practice

Members of BSAC and HIS, with the knowledge of the Councils of each, have been discussing the issues surrounding the recent increase in infections with multi-resistant Gram-negative bacteria in UK hospitals.

Following discussions and consideration of the forthcoming APRHAI report we now believe it an appropriate time to set up a Joint Working Party to look at making authoritative recommendations both for treatment and prevention of transmission of these infections.

2.3. The remit

To examine and make recommendations both for treatment and prevention of transmission of multi-drug-resistant (MDR) Gram-negative infections, resulting in the publication of guidelines on:

- current epidemiology and infection control issues; and
- therapeutic issues and antibiotic guidance for treating infections caused by MDR Gram-negative bacteria.

For the purposes of this Working Party, the remit will mainly include infections in critical and non-critical care patients in secondary care. However, the same general principles would apply in community settings, particularly in areas where inappropriate treatment is encouraging selection. Consideration will be given to laboratory testing and susceptibility testing, although only screening and confirmatory tests available in a general microbiology laboratory. The use of antibiotic combinations in the therapy of infections will be considered, both parenteral and oral agents.

2.4. The Guideline

The guideline development process is described on the NICE website and reproduced in Appendix 3. The Working Party will follow the SIGN process when developing guidance including the hosting of a national stakeholder meeting as part of the national stakeholder consultation process.

2.5. The Scope

Defines what the guideline will and will not examine and what the guideline developers will consider. The scope is based on the referral from the three Societies and is the final scope.

2.5.1. Population Groups that will be covered

a) Adults

Particular consideration given to patients of 65 years and older, and people at high risk of acquiring multi-resistant bacteria such as those requiring care in hospital settings

b) Children over 1 month old

2.5.2. Key clinical issues that will be covered

a) Antimicrobial treatment of MDR Gram-negative infections

b) Antimicrobial stewardship

c) Epidemiology

d) Surveillance

e) Infection prevention: standards, hand and environmental hygiene, organizational structures

Clinical situations that will not be covered include:

Cystic fibrosis

Community outbreaks

2.5.3. Infections that will be covered

Those caused by the following organisms

Escherichia coli, *Klebsiella* spp. including *Klebsiella pneumoniae, Enterobacter* spp., *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Proteus* spp., *Serratia* spp., *Citrobacter freundii, Morganella morgani*

Sexually transmitted infections, *Helicobacter* ssp. *Salmonella* ssp. and some anaerobes are Gram-negative and are increasingly resistant, but were excluded because relevant public health control actions are substantially different or they have not been researched.

2.5.4. Antibiotics that will be considered

Standard antibiotics currently in use such as most cephalosporins, coamoxiclav, piperacillin/tazobactam quinolones, temocillin (pivmecillinam is the oral formulation of mecillinam

Old antibiotics that have been re-introduced: such as aminoglycosides (including gentamicin and amikacin), colistin, fosfomycin, nitrofurantoin

Recently developed antibiotics: tigecycline, cefepime, new B-lactam-B-lactamase inhibitor combinations and carbapenems or those new agents at preliminary stages of testing.

2.5.5. Healthcare settings

All settings in which NHS care is received

2.6. Main outcomes

Outputs will be the production of guidelines, which will be approved via a process of national consultation. The intention is to inform and guide practice but also to highlight areas where more research is needed. The following will be produced and published as indicated:

Current epidemiology and infection control issues – Journal of Hospital Infection
Therapeutic issues and antibiotic guidance for treating infections caused by multi-resistant Gram-negatives – Journal of Antimicrobial Chemotherapy
In addition, it is expected that each Journal will carry a leading article or review article on the guidance that is published by the joint societies.

2.7. Recommendations for practice

Treatment
Surveillance
Screening
Prevention of transmission
Cleaning and environment

2.8. Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions.
Failure to implement the recommendations would result in greater costs in terms of life expectancy or quality. Screening and isolation will result in significant cost pressures where this is not currently practised, but these costs are set against reduced transmission and fewer cases needing antibiotic treatment. Prolonged isolation can have adverse effects on a patient's psychological health, so may have additional unexpected costs.

2.9. Patient Representation and Equality

Patient representatives are invited to all meetings and involved in the writing and drafting of the guidelines. As part of these discussions potential impacts on equality of groups sharing protected characteristics are considered and incorporated into the guidelines. Health inequalities associated with socioeconomic factors and with inequities in access for groups to healthcare and social care are considered and opportunities identified to improve health.

2.10. Status

2.10.1 Scope

This is the final scope.

2.10.2 Timing

The development of the guideline recommendation began in July 2011.

Appendix 3 Guideline development process

3.1. Guidance document

Scottish Intercollegiate Guidelines Network. *SIGN 50: a guideline developer's handbook.* Revised edition. Edinburgh: Healthcare Improvement Scotland; 2014. Available at: http://www.sign.ac.uk [last accessed April 2017].

3.2. Related NICE guidance

National Institute for Health and Care Excellence. Infection: prevention and control of healthcare-associated infections in primary and community care. NICE Clinical Guideline 139. London: NICE; 2012. Last updated: February 2017. Available at: http://www.nice.org.uk/guidance/cg139 [last accessed April 2017].

National Institute for Health and Care Excellence. .Antimicrobial stewardship: prescribing antibiotics. London: NICE; Published date: January 2015 Last updated: January 2017. Available at: https://www.nice.org.uk/advice/ktt9/chapter/evidence-context [last accessed July 2017]

National Institute for Health and Care Excellence. .Urinary Tract Infection in Adults. London: NICE; Quality standard [QS90] Published date: June 2015. Available at: https://www.nice.org.uk/guidance/qs90/chapter/introduction

NICE approved guideline: Wilson AP, Livermore DM, Otter JA, et al. Prevention and control of multi-drug-resistant Gram-negative bacteria: recommendations from a Joint Working Party. *J Hosp Infect* 2016; 92 Suppl 1: S1-S44. Available at : http://www.journalofhospitalinfection.com/article/S0195-6701(15)00314-X/pdf

3.3. Process followed

The subject was identified by the Scientific Development Committee of the Healthcare Infection Society in February 2011 and approved by HIS in May 2011. The BSAC Council agreed a similar proposal at the same time. BIA Council agreed to join in September 2011. The members were chosen to reflect the range of stakeholders and not limited to members of the three Societies. The questions were decided at the first meeting of the

Group in November 2011 from issues presented to the members and patient representatives by staff and patients in the preceding months. Each was debated by the Group before adoption. Enhance Reviews was paid for the serach and data extraction. Working Party members were not paid except for travel expenses.

3.4. Conflict of Interests

Conflicts of interest were registered at the outset and renewed during the process. They are stated in the Transparency declaration of the Report. In the event of a potential conflict being identified, the Working Party agreed that the member should not contribute to the section affected. With one exception, no interests were declared that required any actions and this related to the infection control paper produced by the working party.

3.5. PICO

Patients: All patient groups were included. The guideline is careful not to make recommendations which may prejudice clinical care based on gender, age, ethnicity or socio-economic status.

Interventions: interventions were identified in the literature to generate intervention specific recommendations

Comparisons: comparisons between intervention and standard management were used;

Outcomes were objective referring to length of hospital stay, mortality, rate of acquisition or infection.

3.6. Systematic Review Questions: Infection Control

1. What is the definition of Multidrug Resistant Gram-negative bacilli?
2. What Gram-negative bacilli cause infection control problems?
3. What are the relative contributions of community and hospital acquisition?

4. What is the evidence for reservoir and spread of mulitresistant Gram-negatives in Care Homes and secondary care?
5. What is the role of agricultural use of sewage and antibiotic treatment in veterinary practice in spreading ESBL?
6. What insights has national *E. coli* bacteraemia surveillance provided?
7. What is the role for screening in patients and staff?
8. What organisms should screening include?
9. Who, how and when to screen patients for Multidrug Resistant Gram-negative bacilli?
10. What can be done concerning patients unable to consent to a rectal swab?
11. How frequently does screening need to be performed?
12. Is there evidence for effective interventions on positive patients i.e. can carriage be cleared?
13. Selective decontamination: Why is it not used? Is there a role?
14. When should the environment be sampled?
15. What is the evidence that respiratory equipment contributes to transmission?
16. What national surveillance is performed and how should it be developed?
17. What is the evidence that sensor taps contribute to transmission?
18. Is there any cleaning method more effective than others at removing the Multidrug Resistant Gram-negative bacilli from the environment?
19. What is the evidence that infection control precautions prevent transmission?
20. Are standard infection control measures sufficient to stop transmission?
21. What are the minimum standards to stop spread in public areas, primary care or care homes?
22. Is there evidence for high/low risk areas within a healthcare facility?
23. Are there any organisational structures within a healthcare facility that play a role in the successful control of multi-resistant Gram-negative bacilli?
24. How should we undertake local screening, why is it important and how should it be interpreted?
25. At what point should passive surveillance switch to active surveillance i.e. screening?
26. What is the role of isolation in the care home/hospital settings?

Is there evidence of differences between organisms in respect of transmission, morbidity and mortality:

3.7. Antimicrobial Chemotherapy -Systematic Review Questions

1. What is the clinical importance of carbapenemases versus AmpC and CTX-M strains?
2. What impact have returning travellers made on UK epidemiology?
3. What is the global epidemiology of MDR-GNR?
4. How do Multidrug Resistant Enterobacteriaceae differ from the non-fermenters in terms of their prevalence and associated resistance genes?
5. What is the efficacy of carbapenems, mecillinam, temocillin, fosfomycin and colistin against specific pathogens?
6. What are the recommended antibiotics for community/secondary/tertiary care?
7. What is the threshold level of resistance for changing choice of empirical treatment for urinary infection?

Appendix 4 Systematic Review

4.1. Databases and Search terms Used 23/5/14[i]

4.1.1. Databases

The Cochrane Library; MEDLINE; EMBASE; CINAHL

MeSH Terms See 4.2.

Free text terms. See 4.2.

Search Date: Medline 1946-2014; Embase 1980-2012; CINAHL (1984-2012)

Search Results (Figure 1)

Total number of articles located after duplicates removed = 2523

Sift 1 Criteria

Abstract screening: Systematic review, primary research, infection relates to MDR Gram-negative infection, informs one or more review question

Articles Retrieved

Total number of studies selected = 597

Sift 2 Criteria

Full text confirms that the article is primary research (randomised controlled trial, non-randomised controlled trials, controlled before and after studies, interrupted time series, case control study, case series, prospective cohort, systematic review; informs one or more of the review questions.

Articles selected for appraisal (10 full text publications could not be retrieved)

Total number of studies selected = 49

Critical appraisal

Articles presenting primary research or a systematic review and meeting the sift criteria were critically appraised by two reviewers using SIGN and EPOC criteria. Consensus was achieved through discussion

Accepted and Rejected Evidence

No meta analyses were available

Accepted after critical appraisal 49

Rejected after critical appraisal 0

4.2. Search

4.2.1. CINAHL (January 1984-December 2012)

#	Query	Results
S83	**S48 AND S82**	**275**
S82	S55 OR S56 OR S81	515,966
S81	S57 or S58 or S59 or S60 or S61 or S62 or S63 or S64 or S65 or S66 or S67 or S68 or S69 or S70 or S71 or S72 or S73 or S74 or S75 or S76 or S77 or S78 or S79 or S80	471,263
S80	TI ((time points n3 over) or (time points n3 multiple) or (time points n3 three) or (time points n3 four) or (time points n3 five) or (time points n3 six) or (time points n3 seven) or (time points n3 eight) or (time points n3 nine) or (time points n3 ten) or (time points n3 eleven) or (time points n3 twelve) or (time points n3 month*) or (time points n3 hour*) or (time points n3 day*) or (time points n3 'more than')) or AB ((time points n3 over) or (time points n3 multiple) or (time points n3 three) or (time points n3 four) or (time points n3 five) or (time points n3 six) or (time points n3 seven) or (time points n3 eight) or (time points n3 nine) or (time points n3 ten) or (time points n3 eleven) or (time points n3 twelve) or (time points n3 month*) or (time points n3 hour*) or (time points n3 day*) or (time points n3 'more than'))	1,527
S78	TI (multicentre or multicenter or multi-centre or multi-center) or AB random*	101,899
S77	TI random* OR controlled	94,669
S76	TI (trial or (study n3 aim) or 'our study') or AB ((study n3 aim) or 'our study')	87,121
S75	TI (pre-workshop or preworkshop or post-workshop or postworkshop or (before n3 workshop) or (after n3 workshop)) or AB (pre-workshop or preworkshop or post-workshop or postworkshop or (before n3 workshop) or (after n3 workshop))	283
S74	TI (demonstration project OR demonstration projects OR preimplement* or pre-implement* or post-implement* or postimplement*) or AB (demonstration project OR demonstration projects OR preimplement* or pre-implement* or post-implement* or postimplement*)	1,290

#	Query	Results
S73	(intervention n6 clinician*) or (intervention n6 community) or (intervention n6 complex) or (intervention n6 design*) or (intervention n6 doctor*) or (intervention n6 educational) or (intervention n6 family doctor*) or (intervention n6 family physician*) or (intervention n6 family practitioner*) or (intervention n6 financial) or (intervention n6 GP) or (intervention n6 general practice*) Or (intervention n6 hospital*) or (intervention n6 impact*) Or (intervention n6 improv*) or (intervention n6 individualize*) Or (intervention n6 individualise*) or (intervention n6 individualizing) or (intervention n6 individualising) or (intervention n6 interdisciplin*) or (intervention n6 multicomponent) or (intervention n6 multi-component) or (intervention n6 multidisciplin*) or (intervention n6 multi-disciplin*) or (intervention n6 multifacet*) or (intervention n6 multi-facet*) or (intervention n6 multimodal*) or (intervention n6 multi-modal*) or (intervention n6 personalize*) or(intervention n6 personalise*) or (intervention n6 personalizing) or (intervention n6 personalising) or (intervention n6 pharmaci*) or (intervention n6 pharmacist*) or (intervention n6 pharmacy) or (intervention n6 physician*) or (intervention n6 practitioner*) Or (intervention n6 prescrib*) or (intervention n6 prescription*) or (intervention n6 primary care) or (intervention n6 professional*) or (intervention* n6 provider*) or (intervention* n6 regulatory) or (intervention n6 regulatory) or (intervention n6 tailor*) or (intervention n6 target*) or (intervention n6 team*) or (intervention n6 usual care)	23,198
S72	TI (collaborativ* or collaboration* or tailored or personalised or personalized) or AB (collaborativ* or collaboration* or tailored or personalised or personalized)	38,021
S71	TI pilot	13,958
S70	(MH 'Pilot Studies')	36,433
S69	AB 'before-and-after'	17,437
S68	AB time series	1,670
S67	TI time series	359
S66	AB (before* n10 during or before n10 after) or AU (before* n10 during or before n10 after)	32,982
S65	TI ((time point*) or (period* n4 interrupted) or (period* n4 multiple) or (period* n4 time) or (period* n4 various) or (period* n4 varying) or (period* n4 week*) or (period* n4 month*) or (period* n4 year*)) or AB ((time point*) or (period* n4 interrupted) or (period* n4 multiple) or (period* n4 time) or (period* n4 various) or (period* n4 varying) or (period* n4 week*) or (period* n4 month*) or (period* n4 year*))	51,050

#	Query	Results
S64	TI ((quasi-experiment* or quasiexperiment* or quasi-random* or quasirandom* or quasi control* or quasicontrol* or quasi* W3 method* or quasi* W3 study or quasi* W3 studies or quasi* W3 trial or quasi* W3 design* or experimental W3 method* or experimental W3 study or experimental W3 studies or experimental W3 trial or experimental W3 design*)) or AB ((quasi-experiment* or quasiexperiment* or quasi-random* or quasirandom* or quasi control* or quasicontrol* or quasi* W3 method* or quasi* W3 study or quasi* W3 studies or quasi* W3 trial or quasi* W3 design* or experimental W3 method* or experimental W3 study or experimental W3 studies or experimental W3 trial or experimental W3 design*))	12,758
S63	TI pre w7 post or AB pre w7 post	9,367
S62	MH 'Multiple Time Series' or MH 'Time Series'	1,312
S61	TI ((comparative N2 study) or (comparative N2 studies) or evaluation study or evaluation studies) or AB ((comparative N2 study) or (comparative N2 studies) or evaluation study or evaluation studies)	11,680
S60	MH Experimental Studies or Community Trials or Community Trials or Pretest-Posttest Design + or Quasi-Experimental Studies + Pilot Studies or Policy Studies + Multicenter Studies	34,567
S59	TI (pre-test* or pretest* or posttest* or post-test*) or AB (pre-test* or pretest* or posttest* or 'post test*) OR TI (preimplement*' or pre-implement*) or AB (pre-implement* or preimplement*)	6,868
S58	TI (intervention* or multiintervention* or multi-intervention* or postintervention* or post-intervention* or preintervention* or pre-intervention*) or AB (intervention* or multiintervention* or multi-intervention* or postintervention* or post-intervention* or preintervention* or pre-intervention*)	151,748
S57	(MH 'Quasi-Experimental Studies')	5,747

#	Query	Results
S56	(TI (systematic* n3 review*)) or (AB (systematic* n3 review*)) or (TI (systematic* n3 bibliographic*)) or (AB (systematic* n3 bibliographic*)) or (TI (systematic* n3 literature)) or (AB (systematic* n3 literature)) or (TI (systematic* n3 review*)) or (AB (systematic* n3 review*)) or (TI (comprehensive* n3 literature)) or (AB (comprehensive* n3 literature)) or (TI (comprehensive* n3 bibliographic*)) or (AB (comprehensive* n3 bibliographic*)) or (JN 'Cochrane Database of Systematic Reviews') or (TI (information n2 synthesis)) or (TI (data n2 synthesis)) or (AB (information n2 synthesis)) or (AB (data n2 synthesis)) or (TI (data n2 extract*)) or (AB (data n2 extract*)) or (TI (medline or pubmed or psyclit or cinahl or (psycinfo not 'psycinfo database') or 'web of science' or scopus or embase)) or (AB (medline or pubmed or psyclit or cinahl or (psycinfo not 'psycinfo database') or 'web of science' or scopus or embase)) or (MH 'Systematic Review') or (MH 'Meta Analysis') or (TI (meta-analy* or metaanaly*)) or (AB (meta-analy* or metaanaly*))	59,817
S55	S49 OR S50 OR S51 OR S52 OR S53 OR S54	158,596
S54	TI ('control* N1 clinical' or 'control* N1 group*' or 'control* N1 trial*' or 'control* N1 study' or 'control* N1 studies' or 'control* N1 design*' or 'control* N1 method*') or AB ('control* N1 clinical' or 'control* N1 group*' or 'control* N1 trial*' or 'control* N1 study' or 'control* N1 studies' or 'control* N1 design*' or 'control* N1 method*')	1
S53	TI controlled or AB controlled	68,638
S52	TI random* or AB random*	117,418
S51	TI ('clinical study' or 'clinical studies') or AB ('clinical study' or 'clinical studies')	7,969
S50	(MM 'Clinical Trials+')	10,670
S49	TI ((multicent* n2 design*) or (multicent* n2 study) or (multicent* n2 studies) or (multicent* n2 trial*)) or AB ((multicent* n2 design*) or (multicent* n2 study) or (multicent* n2 studies) or (multicent* n2 trial*))	8,917
S48	S18 AND S21 AND S47	917
S47	S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46	16,726

#	Query	Results
S46	TI ((belcomycin or colicort or colimycin* or colisitin or colisticin or Colistin or colistine or colomycin or (coly n1 mycin) or colymicin or colymycin or coly-mycin or multimycin or (Polymyxin n1 E) or totazina)) OR AB ((belcomycin or colicort or colimycin* or colisitin or colisticin or Colistin or colistine or colomycin or (coly n1 mycin) or colymicin or colymycin or coly-mycin or multimycin or (Polymyxin n1 E) or totazina))	171
S45	(MH 'Colistin')	134
S44	TI (((amdinocillin n1 pivoxil) or (FL n1 '1039') or FL1039 or fl1039 or FL-1039 or pivamdinocillin or Pivmecillinam or Selexid or coactabs or (ro n1 '109071') or (ro10 n1 '9071') or ro109071)) OR AB (((amdinocillin n1 pivoxil) or (FL n1 '1039') or FL1039 or fl1039 or FL-1039 or pivamdinocillin or Pivmecillinam or Selexid or coactabs or (ro n1 '109071') or (ro10 n1 '9071') or ro109071))	13
S43	TI (((Cephalosporanic n1 Acid*) or Cephalosporin* or Cefamandole or Cefoperazone or Cefazolin or Cefonicid or Cefsulodin or Cephacetrile or Cefotaxime or Cephalothin or Cephapirin or Cephalexin or Cefaclor or Cefadroxil or Cephaloglycin or Cephradine or Cephaloridine or Ceftazidime or Cephamycins or Cefmetazole or Cefotetan or Cefoxitin)) OR AB (((Cephalosporanic n1 Acid*) or Cephalosporin* or Cefamandole or Cefoperazone or Cefazolin or Cefonicid or Cefsulodin or Cephacetrile or Cefotaxime or Cephalothin or Cephapirin or Cephalexin or Cefaclor or Cefadroxil or Cephaloglycin or Cephradine or Cephaloridine or Ceftazidime or Cephamycins or Cefmetazole or Cefotetan or Cefoxitin))	1,569
S42	TI ((Axepim* or bmy 28142 or bmy28142 or BMY-28142 or Cefepim* or cefepitax or ceficad or cepimax or forzyn beta or maxcef or maxfrom or maxipime or Quadrocef)) OR AB ((Axepim* or bmy 28142 or bmy28142 or BMY-28142 or Cefepim* or cefepitax or ceficad or cepimax or forzyn beta or maxcef or maxfrom or maxipime or Quadrocef))	171
S41	(MH 'Cephalosporins+')	2,105

#	Query	Results
S40	TI ((berkfurin or biofurin or chemiofuran or dantafur or f 30 or f30 or fua-med or furaben or furadantin* or furadantoin or furadina or furadoine or furadonin or furadonine or furalan or furanpur or furantocompren or furantoin* or furobactina or furofen or furophen or infurin or ituran or ivadantin or macrobid or macrodantin* or macrofuran or macrofurin or micofurantin* or mitrofuratoin or nephronex or nierofu or nifurantin or nifuryl or (nitro n1 macro) or nitrofuracin or nitrofuradantoin or nitrofurantine or nitrofurantoin* or nitrofurin or novofuran or nsc 2107 or nsc2107 or orafuran or parfuran or phenurin or (potassium n1 furagin) or ralodantin or trocurine or urantin or (uro n1 tablinen) or urodil or urodin or urofuran or urolong or urotablinen or uro-tablinen or urotoina or uvamin)) OR AB ((berkfurin or biofurin or chemiofuran or dantafur or f 30 or f30 or fua-med or furaben or furadantin* or furadantoin or furadina or furadoine or furadonin or furadonine or furalan or furanpur or furantocompren or furantoin* or furobactina or furofen or furophen or infurin or ituran or ivadantin or macrobid or macrodantin* or macrofuran or macrofurin or micofurantin* or mitrofuratoin or nephronex or nierofu or nifurantin or nifuryl or (nitro n1 macro) or nitrofuracin or nitrofuradantoin or nitrofurantine or nitrofurantoin* or nitrofurin or novofuran or nsc 2107 or nsc2107 or orafuran or parfuran or phenurin or (potassium n1 furagin) or ralodantin or trocurine or urantin or (uro n1 tablinen) or urodil or urodin or urofuran or urolong or urotablinen or uro-tablinen or urotoina or uvamin))	325
S39	TI (((az n1 threonam) or azactam or azenam or azthreonam or aztreonam or (corus n1 ‘1020’) or dynabiotic or primbactam or SQ 26,776 or sq 26,776 or sq 26776 or SQ-26,776 or sq26776 or sq-26776 or urobactam)) OR AB (((az n1 threonam) or azactam or azenam or azthreonam or aztreonam or (corus n1 ‘1020’) or dynabiotic or primbactam or SQ 26,776 or sq 26,776 or sq 26776 or SQ-26,776 or sq26776 or sq-26776 or urobactam))	96
S38	(MH ‘Aztreonam’)	54
S37	TI ((fosfocil or fosfocin or fosfocina or fosfomicin or fosfomycin or fosfonomycin or ‘mk 0955’ or mk 955 or mk0955 or mk955 or monuril or phosphomycin or phosphonomycin)) OR AB ((fosfocil or fosfocin or fosfocina or fosfomicin or fosfomycin or fosfonomycin or ‘mk 0955’ or mk 955 or mk0955 or mk955 or monuril or phosphomycin or phosphonomycin))	57

#	Query	Results
S36	TI ((akacin or akicin or amicacina or amicasil or amicin or amiglymide v or amikacin* or amikafur or amikalem or amikan or amikayect or amikin or amiklin or amikozit or amiktam or amitracin or amixin or amukin or apalin or bb k 8 or bb k8 or bbk 8 or bb-k 8 or bbk8 or bbk-8 or bb-k8 or biclin or biklin or biokacin or briclin or briklin or chemacin or cinmik or fabianol or gamikal or glukamin or kacinth-a or kanbine or kormakin or likacin or lukadin or miacin or mikasome or onikin or oprad or orlobin or pediakin or pierami or riklinak or savox or selaxa or selemycin or sulfate amikacin or tybikin or vs 107 or vs107 or yectamid)) OR AB ((akacin or akicin or amicacina or amicasil or amicin or amiglymide v or amikacin* or amikafur or amikalem or amikan or amikayect or amikin or amiklin or amikozit or amiktam or amitracin or amixin or amukin or apalin or bb k 8 or bb k8 or bbk 8 or bb-k 8 or bbk8 or bbk-8 or bb-k8 or biclin or biklin or biokacin or briclin or briklin or chemacin or cinmik or fabianol or gamikal or glukamin or kacinth-a or kanbine or kormakin or likacin or lukadin or miacin or mikasome or onikin or oprad or orlobin or pediakin or pierami or riklinak or savox or selaxa or selemycin or sulfate amikacin or tybikin or vs 107 or vs107 or yectamid))	342
S35	(MH ‘Amikacin’)	140

#	Query	Results
S34	TI ((adelanin or alcomicin or apigent or apogen or apoten or azupel or bactiderm or biogaracin or bristagen or cidomycin or danigen or dermogen or dianfarma or dispagent or duragentam* or epigent or (frieso n1 gent) or garabiotic or garalone or garamicin* or garamycin or garbilocin or gencin or gendril or genoptic or genrex or gensumycin or gentabiotic or gentabiox or gentac or gentacidin or gentacin or gentacor or gentacycol or gentacyl or gentafair or gentagram or gentak or gental or gentaline or gentalline or gentalol or gentalyn or gentamax or gentame* or gentamicin* or gentamina or gentamycin* or gentamyl or gentamytrex or gentaplus or gentarad or gentasil or gentasol or gentasone or gentasporin or gentatrim or gentavet or genticin* or genticyn or gentiderm or gentimycin or gentocin or gentogram or gentomycin or genum or geomycine or gevramycin or g-mycin or gmyticin or g-myticin or grammicin or hexamycin or jenamicin or konigen or lacromycin or lisagent or martigenta or migenta or miragenta or miramycin or nichogencin or nsc 82261 or nsc82261 or obogen or ocugenta or ocu-mycin or oftagen or ophtagram or opthagen or optigen or opti-genta or ottogenta or pyogenta or refobacin or ribomicin or rigaminol or rocy gen or rovixida or rupegen or sagestam or sch 9724 or sch9724 or sedanazin or servigenta or skinfect or sulmycin or tangyn or u-gencin or versigen or yectamicina)) OR AB ((adelanin or alcomicin or apigent or apogen or apoten or azupel or bactiderm or biogaracin or bristagen or cidomycin or danigen or dermogen or dianfarma or dispagent or duragentam* or epigent or (frieso n1 gent) or garabiotic or garalone or garamicin* or garamycin or garbilocin or gencin or gendril or genoptic or genrex or gensumycin or gentabiotic or gentabiox or gentac or gentacidin or gentacin or gentacor or gentacycol or gentacyl or gentafair or gentagram or gentak or gental or gentaline or gentalline or gentalol or gentalyn or gentamax or gentame* or gentamicin* or gentamina or gentamycin* or gentamyl or gentamytrex or gentaplus or gentarad or gentasil or gentasol or gentasone or gentasporin or gentatrim or gentavet or genticin* or genticyn or gentiderm or gentimycin or gentocin or gentogram or gentomycin or genum or geomycine or gevramycin or g-mycin or gmyticin or g-myticin or grammicin or hexamycin or jenamicin or konigen or lacromycin or lisagent or martigenta or migenta or miragenta or miramycin or nichogencin or nsc 82261 or nsc82261 or obogen or ocugenta or ocu-mycin or oftagen or ophtagram or opthagen or optigen or opti-genta or ottogenta or pyogenta or refobacin or ribomicin or rigaminol or rocy gen or rovixida or rupegen or sagestam or sch 9724 or sch9724 or sedanazin or servigenta or skinfect or sulmycin or tangyn or u-gencin or versigen or yectamicina))	993
S33	(MH ‘Gentamicins’)	808

#	Query	Results
S32	TI ((Aminoglycosides or Anthracyclines or Aclarubicin or Daunorubicin or Plicamycin or Butirosin Sulfate or Sisomicin or Hygromycin B or Kanamycin or Dibekacin or Nebramycin or Metrizamide or Neomycin or Framycetin or Paromomycin or Ribostamycin or Puromycin or Spectinomycin or Streptomycin or Dihydrostreptomycin Sulfate or Streptothricins or Streptozocin)) OR AB ((Aminoglycosides or Anthracyclines or Aclarubicin or Daunorubicin or Plicamycin or Butirosin Sulfate or Sisomicin or Hygromycin B or Kanamycin or Dibekacin or Nebramycin or Metrizamide or Neomycin or Framycetin or Paromomycin or Ribostamycin or Puromycin or Spectinomycin or Streptomycin or Dihydrostreptomycin Sulfate or Streptothricins or Streptozocin))	1,269
S31	(MH 'Aminoglycosides+')	6,215
S30	TI (((chinolone n1 derivative) or fluoroquinolones or (haloquinolone n1 derivative) or ketoquinolines or oxoquinolines or quinolinones or quinolones)) OR AB (((chinolone n1 derivative) or fluoroquinolones or (haloquinolone n1 derivative) or ketoquinolines or oxoquinolines or quinolinones or quinolones))	834
S29	(MH 'Quinolines+') OR (MH 'Antiinfective Agents, Quinolone+')	4,842
S28	TI ((tigecycline or (tbg n1 mino) or tygacil or gar 936 or gar936 or (tert n1 butylglycinamido*))) OR AB ((tigecycline or (tbg n1 mino) or tygacil or gar 936 or gar936 or (tert n1 butylglycinamido*)))	208
S27	TI (((brl n1 '17421') or brl17421 or (thiophenemalonamic n1 acid) or negaban or temocillin or temopen)) OR AB (((brl n1 '17421') or brl17421 or (thiophenemalonamic n1 acid) or negaban or temocillin or temopen))	10

#	Query	Results
S26	TI ((aclam or aktil or ambilan or amocla or amoclan or amoclav or amoksiklav or amolanic or amometin or (amox n1 clav) or amox-clav or (amoxi n1 plus) or (amoxNear/3clavulan*) or amoxiclav or amoxiclav-bid or amoxiclav-teva or amoxsiklav or amoxxlin or (amoxycillin-clavulanic n1 acid) or ancla or (auclatin n1 duo) or augamox or augmaxcil or augmentan or augmentin* or augmex or augpen or (augucillin n1 duo) or augurcin or ausclav or auspilic or bactiv or bactoclav or bioclavid or (brl n1 '25000') or brl25000 or brl-25000 or cavumox or ciblor or (clacillin n1 duo) or clamax or clamentin or clamobit or clamonex or clamovid or clamoxin or (clamoxyl n1 duo*) or clarin-duo or clavamox or clavar or clavinex or clavodar or clavoxil or (clavoxilin n1 plus) or clavubactin or clavudale or clavulanate-amoxicillin or clavulin or (clavulox n1 duo) or clavumox or (co n1 amoxiclav) or (co n1 amoxyclav) or coamoxiclav or co-amoxiclav or coamoxyclav or (cramon n1 duo) or (croanan n1 duo) or curam or danoclav or (darzitil n1 plus) or e-moxclav or enhancin or fleming or fugentin or (fullicilina n1 plus) or gumentin or hibiotic or inciclav or klamonex or kmoxilin or lactamox or lansiclav or moxiclav or moxicle or moxyclav or natravox or nufaclav or palentin or quali-mentin or ranclav or spektramox or stacillin or suplentin or synermox or synulox or (velamox n1 cl) or vestaclav or viaclav or vulamox or xiclav or (zami n1 '8503'))) OR AB ((aclam or aktil or ambilan or amocla or amoclan or amoclav or amoksiklav or amolanic or amometin or (amox n1 clav) or amox-clav or (amoxi n1 plus) or (amoxNear/3clavulan*) or amoxiclav or amoxiclav-bid or amoxiclav-teva or amoxsiklav or amoxxlin or (amoxycillin-clavulanic n1 acid) or ancla or (auclatin n1 duo) or augamox or augmaxcil or augmentan or augmentin* or augmex or augpen or (augucillin n1 duo) or augurcin or ausclav or auspilic or bactiv or bactoclav or bioclavid or (brl n1 '25000') or brl25000 or brl-25000 or cavumox or ciblor or (clacillin n1 duo) or clamax or clamentin or clamobit or clamonex or clamovid or clamoxin or (clamoxyl n1 duo*) or clarin-duo or clavamox or clavar or clavinex or clavodar or clavoxil or (clavoxilin n1 plus) or clavubactin or clavudale or clavulanate-amoxicillin or clavulin or (clavulox n1 duo) or clavumox or (co n1 amoxiclav) or (co n1 amoxyclav) or coamoxiclav or co-amoxiclav or coamoxyclav or (cramon n1 duo) or (croanan n1 duo) or curam or danoclav or (darzitil n1 plus) or e-moxclav or enhancin or fleming or fugentin or (fullicilina n1 plus) or gumentin or hibiotic or inciclav or klamonex or kmoxilin or lactamox or lansiclav or moxiclav or moxicle or moxyclav or natravox or nufaclav or palentin or quali-mentin or ranclav or spektramox or stacillin or suplentin or synermox or synulox or (velamox n1 cl) or vestaclav or viaclav or vulamox or xiclav or (zami n1 '8503')))	805

#	Query	Results
S25	TI ((cl 307579 or cl298741 or cl307579 or tazabactam or tazobac* or tazocel or tazocillin* or tazocin or tazomax or tazonam or tazopril or yp 14 or yp14 or ytr 830 or ytr 830h or ytr830 or ytr830h or zosyn)) OR AB ((cl 307579 or cl298741 or cl307579 or tazabactam or tazobac* or tazocel or tazocillin* or tazocin or tazomax or tazonam or tazopril or yp 14 or yp14 or ytr 830 or ytr 830h or ytr830 or ytr830h or zosyn))	247
S24	TI ((acopex or avocin or cl 227,193 or Cl 227193 or cl 227193 or cl 227193 or cl227,193 or Cl227193 or cl227193 or cl227193 or Cl-227193 or cl-227193 or cypercil or hishiyaclorin or ivacin or pentcillin or pentocillin or picillin* or pipcil or pipera hameln or piperacil or piperacillin* or piperacin or pipera-hameln or pipercillin or piperilline or pipraci* or pipraks or pipril or piprilin or pitamycin or t 1220 or t1220 or t-1220 or taiperacillin)) OR AB ((acopex or avocin or cl 227,193 or Cl 227193 or cl 227193 or cl 227193 or cl227,193 or Cl227193 or cl227193 or cl227193 or Cl-227193 or cl-227193 or cypercil or hishiyaclorin or ivacin or pentcillin or pentocillin or picillin* or pipcil or pipera hameln or piperacil or piperacillin* or piperacin or pipera-hameln or pipercillin or piperilline or pipraci* or pipraks or pipril or piprilin or pitamycin or t 1220 or t1220 or t-1220 or taiperacillin))	296
S23	TI ((Carbapenem* or doripenem or ertapenem or Imipemide or Imipenem or Invanoz or Invanz or meropenem or Merrem or 'MK 0787' or MK0787 or MK-0787 or N Formimidoylthienamycin or N-Formimidoylthienamycin or Penem or Ronem or S 4661 or S-4661 or SM 7338 or SM-7338 or Thienamycin*)) OR AB ((Carbapenem* or doripenem or ertapenem or Imipemide or Imipenem or Invanoz or Invanz or meropenem or Merrem or 'MK 0787' or MK0787 or MK-0787 or N Formimidoylthienamycin or N-Formimidoylthienamycin or Penem or Ronem or S 4661 or S-4661 or SM 7338 or SM-7338 or Thienamycin*))	974
S22	(MH 'Carbapenems+')	559
S21	S19 OR S20	14,473
S20	(MH 'Drug Resistance, Microbial+')	14,182
S19	TI ((multiresistant or (multi n1 resistan*))) OR AB ((multiresistant or (multi n1 resistan*)))	604
S18	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17	7,706

#	Query	Results
S17	TI (((bacillus n1 morgan*) or (bacterium n1 morgana) or (morganella n1 morgagni*) or (morganella n1 morganii) or (proteus n1 morgagni) or (proteus n1 morgana*) or (salmonella n1 morgana))) OR AB (((bacillus n1 morgan*) or (bacterium n1 morgana) or (morganella n1 morgagni*) or (morganella n1 morganii) or (proteus n1 morgagni) or (proteus n1 morgana*) or (salmonella n1 morgana)))	20
S16	TI (((Citrobacter n1 freundii) or (bacterium n1 freundii) or (Escherichia n1 freundii))) OR AB (((Citrobacter n1 freundii) or (bacterium n1 freundii) or (Escherichia n1 freundii)))	32
S15	(MH 'Citrobacter')	40
S14	TI Serratia OR AB Serratia	238
S13	(MH 'Serratia') OR (MH 'Serratia Infections')	174
S12	TI Proteus OR AB Proteus	257
S11	(MH 'Proteus') OR (MH 'Proteus Infections')	118
S10	TI ((Acinetobacter or mima or mimae or herellea or acinetobacterium)) OR AB ((Acinetobacter or mima or mimae or herellea or acinetobacterium))	889
S9	(MH 'Acinetobacter Infections')	581
S8	TI 'p. aeruginosa' OR AB 'p. aeruginosa'	610
S7	TI (((bacillus n1 pyocyaneus) or (bacterium n1 (aeruginosum or pyocyaneum)) or (blue n1 apus) or (Pseudomonas n1 (aeruginosa or aureofaciens or pyoceaneus or pyocyanea or pyocyaneus)))) OR AB (((bacillus n1 pyocyaneus) or (bacterium n1 (aeruginosum or pyocyaneum)) or (blue n1 apus) or (Pseudomonas n1 (aeruginosa or aureofaciens or pyoceaneus or pyocyanea or pyocyaneus))))	1,855
S6	TI ((enterobacter or aerobacter)) OR AB ((enterobacter or aerobacter))	370
S5	TI (('k. pneumoniae' or 'b. friedlander')) OR AB (('k. pneumoniae' or 'b. friedlander'))	200

#	Query	Results
S4	TI ((klebsiella or Calymmatobacterium or (aerobacter n1 aerogenes) or ((bacillus or bacterium) n1 pneumonia) or ((friedlaender or Friedlander) n1 bacillus) or (Hyalococcus n1 pneumonia) or Pneumobacillus)) OR AB ((klebsiella or Calymmatobacterium or (aerobacter n1 aerogenes) or ((bacillus or bacterium) n1 pneumonia) or ((friedlaender or Friedlander) n1 bacillus) or (Hyalococcus n1 pneumonia) or Pneumobacillus))	1,039
S3	(MH 'Klebsiella') OR (MH 'Klebsiella Infections')	835
S2	TI ((Eaggec or (escherichia n1 coli) or (e n1 coli) or (alkalescens-dispar n1 group) or (bacillus n1 escherichii) or (Coli n1 bacillus) or (Coli n1 bacterium) or colibacillus or (colon n1 bacillus))) OR AB ((Eaggec or (escherichia n1 coli) or (e n1 coli) or (alkalescens-dispar n1 group) or (bacillus n1 escherichii) or (Coli n1 bacillus) or (Coli n1 bacterium) or colibacillus or (colon n1 bacillus)))	2,914
S1	(MH 'Escherichia Coli') OR (MH 'Escherichia Coli Infections')	2,983

4.2.2. Cochrane Library (Issue 11, 2012)

ID Search

#1 MeSH descriptor: [Escherichia coli] explode all trees

#2 (Eaggec or (escherichia near/1 coli) or (e near/1 coli) or (alkalescens-dispar near/1 group) or (bacillus near/1 escherichii) or (Coli near/1 bacillus) or (Coli near/1 bacterium) or colibacillus or (colon near/1 bacillus)):ti,ab,kw (Word variations have been searched)

#3 MeSH descriptor: [Klebsiella] explode all trees

#4 (klebsiella or Calymmatobacterium or (aerobacter near/1 aerogenes) or ((bacillus or bacterium) near/1 pneumonia) or ((friedlaender or Friedlander) near/1 bacillus) or (Hyalococcus near/1 pneumonia) or Pneumobacillus):ti,ab,kw (Word variations have been searched)

#5 k. pneumoniae or b. friedlander:ti,ab,kw (Word variations have been searched)

#6 MeSH descriptor: [Enterobacter] explode all trees

#7 (enterobacter or aerobacter):ti,ab,kw (Word variations have been searched)

#8 MeSH descriptor: [Pseudomonas aeruginosa] explode all trees

#9 ((bacillus near/1 pyocyaneus) or (bacterium near/1 (aeruginosum or pyocyaneum)) or (blue near/1 apus) or (Pseudomonas near/1 (aeruginosa or aureofaciens or pyoceaneus or pyocyanea or pyocyaneus))):ti,ab,kw (Word variations have been searched)

#10 p. aeruginosa:ti,ab,kw (Word variations have been searched)

#11 MeSH descriptor: [Acinetobacter] explode all trees

#12 (Acinetobacter or mima or mimae or herellea or acinetobacterium):ti,ab,kw (Word variations have been searched)

#13 MeSH descriptor: [Proteus] explode all trees

#14 Proteus:ti,ab,kw (Word variations have been searched)

#15 MeSH descriptor: [Serratia] explode all trees

#16 Serratia:ti,ab,kw (Word variations have been searched)

#17 MeSH descriptor: [Citrobacter freundii] explode all trees

#18 ((Citrobacter near/1 freundii) or (bacterium near/1 freundii) or (Escherichia near/1 freundii)):ti,ab,kw (Word variations have been searched)

#19 MeSH descriptor: [Morganella morganii] explode all trees

#20 ((bacillus near/1 morgan$) or (bacterium near/1 morgana) or (morganella near/1 morgagni$) or (morganella near/1 morganii) or (proteus near/1 morgagni) or (proteus near/1 morgana$) or (salmonella near/1 morgana)):ti,ab,kw (Word variations have been searched)

#21 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20

#22 (multiresistant or (multi near/1 resistan$)):ti,ab,kw (Word variations have been searched)

#23 MeSH descriptor: [Drug Resistance, Multiple] explode all trees

#24 #22 or #23

#25 MeSH descriptor: [Colistin] explode all trees

#26 (belcomycin or colicort or colimycin$ or colisitin or colisticin or Colistin or colistine or colomycin or (coly near/1 mycin) or colymicin or colymycin or coly-mycin or multimycin or (Polymyxin near/1 E) or totazina):ti,ab,kw (Word variations have been searched)

#27 MeSH descriptor: [Carbapenems] explode all trees

#28 (Carbapenem$ or doripenem or ertapenem or Imipemide or Imipenem or Invanoz or Invanz or meropenem or Merrem or 'MK 0787' or MK0787 or MK-0787 or N Formimidoylthienamycin or N-Formimidoylthienamycin or Penem or Ronem or S 4661 or S-4661 or SM 7338 or SM-7338 or Thienamycin$):ti,ab,kw (Word variations have been searched)

#29 MeSH descriptor: [Piperacillin] explode all trees

#30 (acopex or avocin or cl 227,193 or Cl 227193 or cl 227193 or cl 227193 or cl227,193 or Cl227193 or cl227193 or cl227193 or Cl-227193 or cl-227193 or cypercil or hishiyaclorin or ivacin or pentcillin or pentocillin or picillin$ or pipcil or pipera hameln or piperacil or piperacillin$ or piperacin or pipera-hameln or pipercillin or piperilline or pipraci$ or pipraks or pipril or piprilin or pitamycin or t 1220 or t1220 or t-1220 or taiperacillin):ti,ab,kw (Word variations have been searched)

#31 (cl 307579 or cl298741 or cl307579 or tazabactam or tazobac$ or tazocel or tazocillin$ or tazocin or tazomax or tazonam or tazopril or yp 14 or yp14 or ytr 830 or ytr 830h or ytr830 or ytr830h or zosyn):ti,ab,kw (Word variations have been searched)

#32 MeSH descriptor: [Amoxicillin-Potassium Clavulanate Combination] explode all trees

#33 (aclam or aktil or ambilan or amocla or amoclan or amoclav or amoksiklav or amolanic or amometin or (amox near/1 clav) or amox-clav or (amoxi near/1 plus) or (amoxNear/3clavulan$) or amoxiclav or amoxiclav-bid or amoxiclav-teva or amoxsiklav or amoxxlin or (amoxycillin-clavulanic near/1 acid) or ancla or (auclatin near/1 duo) or augamox or augmaxcil or augmentan or augmentin$ or augmex or augpen or (augucillin near/1 duo) or augurcin or ausclav or auspilic or bactiv or bactoclav or bioclavid or (brl near/1 '25000') or brl25000 or brl-25000 or cavumox or ciblor or (clacillin near/1 duo) or clamax or clamentin or clamobit or clamonex or clamovid or clamoxin or (clamoxyl near/1 duo$) or clarin-duo or clavamox or clavar or clavinex or clavodar or clavoxil or (clavoxilin near/1 plus) or clavubactin or clavudale or clavulanate-amoxicillin or clavulin or (clavulox near/1 duo) or clavumox or (co near/1 amoxiclav) or (co near/1 amoxyclav) or coamoxiclav or co-amoxiclav or coamoxyclav or (cramon near/1 duo) or (croanan near/1 duo) or curam or danoclav or (darzitil near/1 plus) or e-moxclav or enhancin or fleming or fugentin or (fullicilina near/1 plus) or gumentin or hibiotic or inciclav or klamonex or kmoxilin or lactamox or lansiclav or moxiclav or moxicle or moxyclav or natravox or nufaclav or palentin or quali-mentin or ranclav or spektramox or stacillin or suplentin or synermox or synulox or (velamox near/1 cl) or vestaclav or viaclav or vulamox or xiclav or (zami near/1 '8503')):ti,ab,kw (Word variations have been searched)

#34 ((brl near/1 '17421') or brl17421 or (thiophenemalonamic near/1 acid) or negaban or temocillin or temopen):ti,ab,kw (Word variations have been searched)

#35 (tigecycline or (tbg near/1 mino) or tygacil or gar 936 or gar936 or (tert near/1 butylglycinamido$)):ti,ab,kw (Word variations have been searched)

#36 MeSH descriptor: [Quinolones] explode all trees

#37 ((chinolone near/1 derivative) or fluoroquinolones or (haloquinolone near/1 derivative) or ketoquinolines or oxoquinolines or quinolinones or quinolones):ti,ab,kw (Word variations have been searched)

#38 MeSH descriptor: [Aminoglycosides] explode all trees

#39 (Aminoglycosides or Anthracyclines or Aclarubicin or Daunorubicin or Plicamycin or Butirosin Sulfate or Sisomicin or Hygromycin B or Kanamycin or Dibekacin or Nebramycin or Metrizamide or Neomycin or Framycetin or Paromomycin or Ribostamycin or Puromycin or Spectinomycin or Streptomycin or Dihydrostreptomycin Sulfate or Streptothricins or Streptozocin):ti,ab,kw (Word variations have been searched)

#40 MeSH descriptor: [Gentamicins] explode all trees

#41 (adelanin or alcomicin or apigent or apogen or apoten or azupel or bactiderm or biogaracin or bristagen or cidomycin or danigen or dermogen or dianfarma or dispagent or duragentam$ or epigent or (frieso near/1 gent) or garabiotic or garalone or garamicin$ or garamycin or garbilocin or gencin or gendril or genoptic or genrex or gensumycin or gentabiotic or gentabiox or gentac or gentacidin or gentacin or gentacor or gentacycol or gentacyl or gentafair or gentagram or gentak or gental or gentaline or gentalline or gentalol or gentalyn or gentamax or gentame$ or gentamicin$ or gentamina or gentamycin$ or gentamyl or gentamytrex or gentaplus or gentarad or

gentasil or gentasol or gentasone or gentasporin or gentatrim or gentavet or genticin$ or genticyn or gentiderm or gentimycin or gentocin or gentogram or gentomycin or genum or geomycine or gevramycin or g-mycin or gmyticin or g-myticin or grammicin or hexamycin or jenamicin or konigen or lacromycin or lisagent or martigenta or migenta or miragenta or miramycin or nichogencin or nsc 82261 or nsc82261 or obogen or ocugenta or ocu-mycin or oftagen or ophtagram or opthagen or optigen or opti-genta or ottogenta or pyogenta or refobacin or ribomicin or rigaminol or rocy gen or rovixida or rupegen or sagestam or sch 9724 or sch9724 or sedanazin or servigenta or skinfect or sulmycin or tangyn or u-gencin or versigen or yectamicina):ti,ab,kw (Word variations have been searched)

#42 MeSH descriptor: [Amikacin] explode all trees

#43 (akacin or akicin or amicacina or amicasil or amicin or amiglymide v or amikacin$ or amikafur or amikalem or amikan or amikayect or amikin or amiklin or amikozit or amiktam or amitracin or amixin or amukin or apalin or bb k 8 or bb k8 or bbk 8 or bb-k 8 or bbk8 or bbk-8 or bb-k8 or biclin or biklin or biokacin or briclin or briklin or chemacin or cinmik or fabianol or gamikal or glukamin or kacinth-a or kanbine or kormakin or likacin or lukadin or miacin or mikasome or onikin or oprad or orlobin or pediakin or pierami or riklinak or savox or selaxa or selemycin or sulfate amikacin or tybikin or vs 107 or vs107 or yectamid):ti,ab,kw (Word variations have been searched)

#44 MeSH descriptor: [Fosfomycin] explode all trees

#45 (fosfocil or fosfocin or fosfocina or fosfomicin or fosfomycin or fosfonomycin or 'mk 0955' or mk 955 or mk0955 or mk955 or monuril or phosphomycin or phosphonomycin):ti,ab,kw (Word variations have been searched)

#46 MeSH descriptor: [Aztreonam] explode all trees

#47 ((az near/1 threonam) or azactam or azenam or azthreonam or aztreonam or (corus near/1 '1020') or dynabiotic or primbactam or SQ 26,776 or sq 26,776 or sq 26776 or SQ-26,776 or sq26776 or sq-26776 or urobactam):ti,ab,kw (Word variations have been searched)

#48 MeSH descriptor: [Nitrofurantoin] explode all trees

#49 (berkfurin or biofurin or chemiofuran or dantafur or f 30 or f30 or fua-med or furaben or furadantin$ or furadantoin or furadina or furadoine or furadonin or furadonine or furalan or furanpur or furantocompren or furantoin$ or furobactina or furofen or furophen or infurin or ituran or ivadantin or macrobid or macrodantin$ or macrofuran or macrofurin or micofurantin$ or mitrofuratoin or nephronex or nierofu or nifurantin or nifuryl or (nitro near/1 macro) or nitrofuracin or nitrofuradantoin or nitrofurantine or nitrofurantoin$ or nitrofurin or novofuran or nsc 2107 or nsc2107 or orafuran or parfuran or phenurin or (potassium near/1 furagin) or ralodantin or trocurine or urantin or (uro near/1 tablinen) or urodil or urodin or urofuran or urolong or urotablinen or uro-tablinen or urotoina or uvamin):ti,ab,kw (Word variations have been searched)

#50 MeSH descriptor: [Cephalosporins] explode all trees

#51 ((Cephalosporanic near/1 Acid$) or Cephalosporin$ or Cefamandole or Cefoperazone or Cefazolin or Cefonicid or Cefsulodin or Cephacetrile or Cefotaxime or Cephalothin or Cephapirin or Cephalexin or Cefaclor or Cefadroxil or Cephaloglycin or

Cephradine or Cephaloridine or Ceftazidime or Cephamycins or Cefmetazole or Cefotetan or Cefoxitin):ti,ab,kw (Word variations have been searched)

#52 MeSH descriptor: [Amdinocillin Pivoxil] explode all trees

#53 ((amdinocillin near/1 pivoxil) or (FL near/1 '1039') or FL1039 or fl1039 or FL-1039 or pivamdinocillin or Pivmecillinam or Selexid or coactabs or (ro near/1 '109071') or (ro10 near/1 '9071') or ro109071):ti,ab,kw (Word variations have been searched)

#54 #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53

#55 #21 and #24 and #54 (21)

4.2.3. Embase (January 1980 to December 1012)

1 exp Escherichia coli/ (255846)

2 (Eaggec or (escherichia adj coli) or (e adj coli) or (alkalescens-dispar adj group) or (bacillus adj escherichii) or (Coli adj bacillus) or (Coli adj bacterium) or colibacillus or (colon adj bacillus)).ti,ab. (240749)

3 exp Klebsiella/ (30199)

4 (klebsiella or Calymmatobacterium or (aerobacter adj aerogenes) or ((bacillus or bacterium) adj pneumonia) or ((friedlaender or Friedlander) adj bacillus) or (Hyalococcus adj pneumonia) or Pneumobacillus).ti,ab. (22836)

5 ('k. pneumoniae' or 'b. friedlander').ti,ab. (5513)

6 exp Enterobacter/ (12784)

7 (enterobacter or aerobacter).ti,ab. (9700)

8 exp Pseudomonas aeruginosa/ (55073)

9 ((bacillus adj pyocyaneus) or (bacterium adj (aeruginosum or pyocyaneum)) or (blue adj apus) or (Pseudomonas adj (aeruginosa or aureofaciens or pyoceaneus or pyocyanea or pyocyaneus))).ti,ab. (43474)

10 'p. aeruginosa'.ti,ab. (17572)

11 exp Acinetobacter/ (12028)

12 (Acinetobacter or mima or mimae or herellea or acinetobacterium).ti,ab. (10917)

13 exp Proteus/ (14447)

14 Proteus.ti,ab. (10461)

15 exp Serratia/ (9507)

16 Serratia.ti,ab. (7407)

17 exp Citrobacter freundii/ (1778)

18 ((Citrobacter adj freundii) or (bacterium adj freundii) or (Escherichia adj freundii)).ti,ab. (1675)

19 exp Morganella morganii/ (1134)

20 ((bacillus adj morgan$) or (bacterium adj morgana) or (morganella adj morgagni$) or (morganella adj morganii) or (proteus adj morgagni) or (proteus adj morgana$) or (salmonella adj morgana)).ti,ab. (804)

21 or/1-20 (396800)

22 (multiresistant or (multi adj resistan$)).ti,ab. (5599)

23 exp multidrug resistance/ (29629)

24 22 or 23 (33705)

25 exp Colistin/ (8049)

26 (belcomycin or colicort or colimycin$ or colisitin or colisticin or Colistin or colistine or colomycin or (coly adj mycin) or colymicin or colymycin or coly-mycin or multimycin or (Polymyxin adj E) or totazina).ti,ab. (3104)

27 exp Carbapenems/ (4745)

28 (Carbapenem$ or doripenem or ertapenem or Imipemide or Imipenem or Invanoz or Invanz or meropenem or Merrem or 'MK 0787' or MK0787 or MK-0787 or N Formimidoylthienamycin or N-Formimidoylthienamycin or Penem or Ronem or S 4661 or S-4661 or SM 7338 or SM-7338 or Thienamycin$).ti,ab. (18086)

29 exp Piperacillin/ (14822)

30 (acopex or avocin or cl 227,193 or Cl 227193 or cl 227193 or cl 227193 or cl227,193 or Cl227193 or cl227193 or cl227193 or Cl-227193 or cl-227193 or cypercil or hishiyaclorin or ivacin or pentcillin or pentocillin or picillin$ or pipcil or pipera hameln or piperacil or piperacillin$ or piperacin or pipera-hameln or pipercillin or piperilline or pipraci$ or pipraks or pipril or piprilin or pitamycin or t 1220 or t1220 or t-1220 or taiperacillin).ti,ab. (6462)

31 exp Amoxicillin-Potassium Clavulanate Combination/ (23616)

32 (aclam or aktil or ambilan or amocla or amoclan or amoclav or amoksiklav or amolanic or amometin or (amox adj clav) or amox-clav or (amoxi adj plus) or (amox adj3 clavulan$) or amoxiclav or amoxiclav-bid or amoxiclav-teva or amoxsiklav or amoxxlin or (amoxycillin-clavulanic adj acid) or ancla or (auclatin adj duo) or augamox or augmaxcil or augmentan or augmentin$ or augmex or augpen or (augucillin adj duo) or augurcin or ausclav or auspilic or bactiv or bactoclav or bioclavid or (brl adj '25000') or brl25000 or brl-25000 or cavumox or ciblor or (clacillin adj duo) or clamax or clamentin or clamobit or clamonex or clamovid or clamoxin or (clamoxyl adj duo$) or clarin-duo or clavamox or clavar or clavinex or clavodar or clavoxil or (clavoxilin adj plus) or clavubactin or clavudale or clavulanate-amoxicillin or clavulin or (clavulox adj duo) or clavumox or (co adj amoxiclav) or (co adj amoxyclav) or coamoxiclav or co-amoxiclav or coamoxyclav or (cramon adj duo) or (croanan adj duo) or curam or danoclav or (darzitil adj plus) or e-moxclav or enhancin or fleming or fugentin or (fullicilina adj plus) or gumentin or hibiotic or inciclav or klamonex or kmoxilin or lactamox or lansiclav or moxiclav or moxicle or moxyclav or natravox or nufaclav or palentin or quali-mentin or ranclav or spektramox or stacillin or suplentin or synermox or synulox or (velamox adj cl) or vestaclav or viaclav or vulamox or xiclav or (zami adj '8503')).ti,ab. (11598)

33 exp Quinolones/ (101072)

34 ((chinolone adj derivative) or fluoroquinolones or (haloquinolone adj derivative) or ketoquinolines or oxoquinolines or quinolinones or quinolones).ti,ab. (15677)

35 exp Aminoglycosides/ (10599)

36 (Aminoglycosides or Anthracyclines or Aclarubicin or Daunorubicin or Plicamycin or Butirosin Sulfate or Sisomicin or Hygromycin B or Kanamycin or Dibekacin or Nebramycin + or Metrizamide or Neomycin or Framycetin or Paromomycin or Ribostamycin or Puromycin or Spectinomycin or Streptomycin or Dihydrostreptomycin Sulfate or Streptothricins or Streptozocin).ti,ab. (56708)

37 exp Gentamicins/ (70647)

38 (adelanin or alcomicin or apigent or apogen or apoten or azupel or bactiderm or biogaracin or bristagen or cidomycin or danigen or dermogen or dianfarma or dispagent or duragentam$ or epigent or (frieso adj gent) or garabiotic or garalone or garamicin$ or garamycin or garbilocin or gencin or gendril or genoptic or genrex or gensumycin or gentabiotic or gentabiox or gentac or gentacidin or gentacin or gentacor or gentacycol or gentacyl or gentafair or gentagram or gentak or gental or gentaline or gentalline or gentalol or gentalyn or gentamax or gentame$ or gentamicin$ or gentamina or gentamycin$ or gentamyl or gentamytrex or gentaplus or gentarad or gentasil or gentasol or gentasone or gentasporin or gentatrim or gentavet or genticin$ or genticyn or gentiderm or gentimycin or gentocin or gentogram or gentomycin or genum or geomycine or gevramycin or g-mycin or gmyticin or g-myticin or grammicin or hexamycin or jenamicin or konigen or lacromycin or lisagent or martigenta or migenta or miragenta or miramycin or nichogencin or nsc 82261 or nsc82261 or obogen or ocugenta or ocu-mycin or oftagen or ophtagram or opthagen or optigen or opti-genta or ottogenta or pyogenta or refobacin or ribomicin or rigaminol or rocy gen or rovixida or rupegen or sagestam or sch 9724 or sch9724 or sedanazin or servigenta or skinfect or sulmycin or tangyn or u-gencin or versigen or yectamicina).ti,ab. (23700)

39 exp Amikacin/ (28644)

40 (akacin or akicin or amicacina or amicasil or amicin or amiglymide v or amikacin$ or amikafur or amikalem or amikan or amikayect or amikin or amiklin or amikozit or amiktam or amitracin or amixin or amukin or apalin or bb k 8 or bb k8 or bbk 8 or bb-k 8 or bbk8 or bbk-8 or bb-k8 or biclin or biklin or biokacin or briclin or briklin or chemacin or cinmik or fabianol or gamikal or glukamin or kacinth-a or kanbine or kormakin or likacin or lukadin or miacin or mikasome or onikin or oprad or orlobin or pediakin or pierami or riklinak or savox or selaxa or selemycin or sulfate amikacin or tybikin or vs 107 or vs107 or yectamid).ti,ab. (9841)

41 exp Fosfomycin/ (5561)

42 (fosfocil or fosfocin or fosfocina or fosfomicin or fosfomycin or fosfonomycin or ‘mk 0955’ or mk 955 or mk0955 or mk955 or monuril or phosphomycin or phosphonomycin).ti,ab. (2386)

43 exp Aztreonam/ (10567)

44 ((az adj threonam) or azactam or azenam or azthreonam or aztreonam or (corus adj ‘1020’) or dynabiotic or primbactam or SQ 26,776 or sq 26,776 or sq 26776 or SQ-26,776 or sq26776 or sq-26776 or urobactam).ti,ab. (3245)

45 exp Nitrofurantoin/ (9724)

46 (berkfurin or biofurin or chemiofuran or dantafur or f 30 or f30 or fua-med or furaben or furadantin$ or furadantoin or furadina or furadoine or furadonin or furadonine or furalan or furanpur or furantocompren or furantoin$ or furobactina or furofen or furophen or infurin or ituran or ivadantin or macrobid or macrodantin$ or macrofuran or macrofurin or micofurantin$ or mitrofuratoin or nephronex or nierofu or nifurantin or nifuryl or (nitro adj macro) or nitrofuracin or nitrofuradantoin or nitrofurantine or nitrofurantoin$ or nitrofurin or novofuran or nsc 2107 or nsc2107 or orafuran or parfuran or phenurin or (potassium adj furagin) or ralodantin or trocurine or urantin or (uro adj tablinen) or urodil or urodin or urofuran or urolong or urotablinen or uro-tablinen or urotoina or uvamin).ti,ab. (3412)

47 exp Cephalosporins/ (150937)

48 (Axepim$ or bmy 28142 or bmy28142 or BMY-28142 or Cefepim$ or cefepitax or ceficad or cepimax or forzyn beta or maxcef or maxfrom or maxipime or Quadrocef).ti,ab. (2995)

49 exp tazobactam/ (3045)

50 (cl 307579 or cl298741 or cl307579 or tazabactam or tazobac$ or tazocel or tazocillin$ or tazocin or tazomax or tazonam or tazopril or yp 14 or yp14 or ytr 830 or ytr 830h or ytr830 or ytr830h or zosyn).ti,ab. (3809)

51 exp temocillin/ (499)

52 ((brl adj '17421') or brl17421 or (thiophenemalonamic adj acid) or negaban or temocillin or temopen).ti,ab. (236)

53 exp tigecycline/ (3876)

54 (tigecycline or (tbg adj mino) or tygacil or gar 936 or gar936 or (tert adj butylglycinamido$)).ti,ab. (1970)

55 exp cefepime/ (9948)

56 ((Cephalosporanic adj Acid$) or Cephalosporin$ or Cefamandole or Cefoperazone or Cefazolin or Cefonicid or Cefsulodin or Cephacetrile or Cefotaxime or Cephalothin or Cephapirin or Cephalexin or Cefaclor or Cefadroxil or Cephaloglycin or Cephradine or Cephaloridine or Ceftazidime or Cephamycins or Cefmetazole or Cefotetan or Cefoxitin).ti,ab. (45983)

57 exp pivmecillinam/ (685)

58 ((amdinocillin adj pivoxil) or (FL adj '1039') or FL1039 or fl1039 or FL-1039 or pivamdinocillin or Pivmecillinam or Selexid or coactabs or (ro adj '109071') or (ro10 adj '9071') or ro109071).ti,ab. (280)

59 or/25-58 (349366)

60 21 and 24 and 59 (4969)

61 (review or review,tutorial or review, academic).pt. (1901059)

62 (systematic$ adj5 review$).tw,sh. (70959)

63 (systematic$ adj5 overview$).tw,sh. (869)

64 (quantitativ$ adj5 review$).tw,sh. (15516)

65 (quantitativ$ adj5 overview$).tw,sh. (203)

66 (quantitativ$ adj5 synthesis$).tw,sh. (2716)
67 (methodologic$ adj5 review$).tw,sh. (3414)
68 (methodologic$ adj5 overview$).tw,sh. (238)
69 (integrative research review$ or research integration).tw. (94)
70 (meta-analys$ or meta analys$ or metaanalys$).tw,sh. (96394)
71 (meta synthesis or meta synthesis or metasynthesis).tw,sh. (238)
72 (meta-regression or meta regression or metaregression).tw,sh. (2242)
73 (synthes$ adj3 literature).tw. (1448)
74 (synthes$ adj3 evidence).tw. (3583)
75 integrative review.tw. (604)
76 data synthesis.tw. (8747)
77 (research synthesis or narrative synthesis).tw. (547)
78 (systematic study or systematic studies).tw. (7413)
79 systematic comparison$.tw. (1183)
80 comprehensive review$.tw. (6873)
81 critical review.tw. (11216)
82 quantitative review.tw. (488)
83 structured review.tw. (492)
84 realist review.tw. (34)
85 realist synthesis.tw. (12)
86 review.ti. (264011)
87 systematic$ literature review$.tw. (3464)
88 'systematic review'/ (55637)
89 'systematic review (topic)'/ (2885)
90 meta analysis/ (67746)
91 'meta analysis (topic)'/ (5552)
92 (synthes$ adj2 qualitative).tw. (428)
93 (systematic adj2 search$).tw. (7848)
94 systematic$ literature research$.tw. (102)
95 (review adj3 scientific literature).tw. (833)
96 (literature review adj2 side effect$).tw. (10)
97 (literature review adj2 adverse effect$).tw. (2)
98 (literature review adj2 adverse event$).tw. (6)
99 (evidence-based adj2 review).tw. (1915)
100 critical analysis.tw. (5559)

101 (review$ adj10 (papers or trials or trial data or studies or evidence or intervention$ or evaluation$ or outcome$ or findings)).tw. (248295)

102 review.ti. (264011)

103 metanaly$.tw. (316)

104 letter.pt. (800258)

105 editorial.pt. (417835)

106 104 or 105 (1218093)

107 or/61-103 (2212977)

108 107 not 106 (2200787)

109 (clin$ adj2 trial).mp. (968683)

110 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).mp. (190403)

111 (random$ adj5 (assign$ or allocat$)).mp. (101920)

112 randomi$.mp. (613392)

113 crossover.mp. (59181)

114 exp randomized-controlled-trial/ (334017)

115 exp double-blind-procedure/ (112280)

116 exp crossover-procedure/ (35737)

117 exp single-blind-procedure/ (16758)

118 exp randomization/ (60197)

119 or/109-118 (1282139)

120 intervention?.ti. or (intervention? adj6 (clinician? or collaborat$ or community or complex or DESIGN$ or doctor? or educational or family doctor? or family physician? or family practitioner? or financial or GP or general practice? or hospital? or impact? or improv$ or individuali?e? or individuali?ing or interdisciplin$ or multicomponent or multi-component or multidisciplin$ or multi-disciplin$ or multifacet$ or multi-facet$ or multimodal$ or multi-modal$ or personali?e? or personali?ing or pharmacies or pharmacist? or pharmacy or physician? or practitioner? or prescrib$ or prescription? or primary care or professional$ or provider? or regulatory or regulatory or tailor$ or target$ or team$ or usual care)).ab. (175033)

121 (hospital$ or patient?).hw. and (study or studies or care or health$ or practitioner? or provider? or physician? or nurse? or nursing or doctor?).ti,hw. (1363115)

122 demonstration project?.ti,ab. (2081)

123 (pre-post or 'pre test$' or pretest$ or posttest$ or 'post test$' or (pre adj5 post)).ti,ab. (78013)

124 (pre-workshop or post-workshop or (before adj3 workshop) or (after adj3 workshop)).ti,ab. (673)

125 trial.ti. or ((study adj3 aim?) or 'our study').ab. (724065)

126 (before adj10 (after or during)).ti,ab. (394152)

127 (time points adj3 (over or multiple or three or four or five or six or seven or eight or nine or ten or eleven or twelve or month$ or hour? or day? or 'more than')).ab. (10006)

128 pilot.ti. (43036)

129 (multicentre or multicenter or multi-centre or multi-center).ti. (34428)

130 random$.ti,ab. or controlled.ti. (819713)

131 review.ti. (264011)

132 *experimental design/ or *pilot study/ or quasi experimental study/ (5205)

133 ('quasi-experiment$' or quasiexperiment$ or 'quasi random$' or quasirandom$ or 'quasi control$' or quasicontrol$ or ((quasi$ or experimental) adj3 (method$ or study or trial or design$))).ti,ab. (105122)

134 or/120-133 (3341084)

135 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ (18985259)

136 human/ or normal human/ or human cell/ (14037258)

137 135 and 136 (14004971)

138 135 not 137 (4980288)

139 ('time series' adj2 interrupt$).ti,ab. (922)

140 134 not (138 or 139) (2996658)

141 108 or 119 or 140 (5157863)

142 and 141 (1860)

4.2.4. Medline (January 1946 to December 2012)

1 exp Escherichia coli/ (224545)

2 (Eaggec or (escherichia adj coli) or (e adj coli) or (alkalescens-dispar adj group) or (bacillus adj escherichii) or (Coli adj bacillus) or (Coli adj bacterium) or colibacillus or (colon adj bacillus)).ti,ab. (226847)

3 exp Klebsiella/ (13720)

4 (klebsiella or Calymmatobacterium or (aerobacter adj aerogenes) or ((bacillus or bacterium) adj pneumonia) or ((friedlaender or Friedlander) adj bacillus) or (Hyalococcus adj pneumonia) or Pneumobacillus).ti,ab. (18345)

5 ('k. pneumoniae' or 'b. friedlander').ti,ab. (3902)

6 exp Enterobacter/ (5504)

7 (enterobacter or aerobacter).ti,ab. (8130)

8 exp Pseudomonas aeruginosa/ (30232)

9 ((bacillus adj pyocyaneus) or (bacterium adj (aeruginosum or pyocyaneum)) or (blue adj apus) or (Pseudomonas adj (aeruginosa or aureofaciens or pyoceaneus or pyocyanea or pyocyaneus))).ti,ab. (35984)

10 'p. aeruginosa'.ti,ab. (14103)

11 exp Acinetobacter/ (5262)

12 (Acinetobacter or mima or mimae or herellea or acinetobacterium).ti,ab. (8005)

13 exp Proteus/ (8091)

14 Proteus.ti,ab. (9496)

15 exp Serratia/ (5505)

16 Serratia.ti,ab. (6720)

17 exp Citrobacter freundii/ (438)

18 ((Citrobacter adj freundii) or (bacterium adj freundii) or (Escherichia adj freundii)).ti,ab. (1361)

19 exp Morganella morganii/ (133)

20 ((bacillus adj morgan$) or (bacterium adj morgana) or (morganella adj morgagni$) or (morganella adj morganii) or (proteus adj morgagni) or (proteus adj morgana$) or (salmonella adj morgana)).ti,ab. (601)

21 or/1-20 (360253)

22 (multiresistant or (multi adj resistan$)).ti,ab. (3949)

23 exp drug resistance, multiple/ (21763)

24 22 or 23 (24405)

25 exp Colistin/ (2107)

26 (belcomycin or colicort or colimycin$ or colisitin or colisticin or Colistin or colistine or colomycin or (coly adj mycin) or colymicin or colymycin or coly-mycin or multimycin or (Polymyxin adj E) or totazina).ti,ab. (2346)

27 exp Carbapenems/ (6668)

28 (Carbapenem$ or doripenem or ertapenem or Imipemide or Imipenem or Invanoz or Invanz or meropenem or Merrem or 'MK 0787' or MK0787 or MK-0787 or N Formimidoylthienamycin or N-Formimidoylthienamycin or Penem or Ronem or S 4661 or S-4661 or SM 7338 or SM-7338 or Thienamycin$).ti,ab. (11771)

29 exp Piperacillin/ (2035)

30 (acopex or avocin or cl 227,193 or Cl 227193 or cl 227193 or cl 227193 or cl227,193 or Cl227193 or cl227193 or cl227193 or Cl-227193 or cl-227193 or cypercil or hishiyaclorin or ivacin or pentcillin or pentocillin or picillin$ or pipcil or pipera hameln or piperacil or piperacillin$ or piperacin or pipera-hameln or pipercillin or piperilline or pipraci$ or pipraks or pipril or piprilin or pitamycin or t 1220 or t1220 or t-1220 or taiperacillin).ti,ab. (4319)

31 (cl 307579 or cl298741 or cl307579 or tazabactam or tazobac$ or tazocel or tazocillin$ or tazocin or tazomax or tazonam or tazopril or yp 14 or yp14 or ytr 830 or ytr 830h or ytr830 or ytr830h or zosyn).ti,ab. (2217)

32 exp Amoxicillin-Potassium Clavulanate Combination/ (1914)

33 (aclam or aktil or ambilan or amocla or amoclan or amoclav or amoksiklav or amolanic or amometin or (amox adj clav) or amox-clav or (amoxi adj plus) or (amox adj3 clavulan$) or amoxiclav or amoxiclav-bid or amoxiclav-teva or amoxsiklav or

amoxxlin or (amoxycillin-clavulanic adj acid) or ancla or (auclatin adj duo) or augamox or augmaxcil or augmentan or augmentin$ or augmex or augpen or (augucillin adj duo) or augurcin or ausclav or auspilic or bactiv or bactoclav or bioclavid or (brl adj '25000') or brl25000 or brl-25000 or cavumox or ciblor or (clacillin adj duo) or clamax or clamentin or clamobit or clamonex or clamovid or clamoxin or (clamoxyl adj duo$) or clarin-duo or clavamox or clavar or clavinex or clavodar or clavoxil or (clavoxilin adj plus) or clavubactin or clavudale or clavulanate-amoxicillin or clavulin or (clavulox adj duo) or clavumox or (co adj amoxiclav) or (co adj amoxyclav) or coamoxiclav or co-amoxiclav or coamoxyclav or (cramon adj duo) or (croanan adj duo) or curam or danoclav or (darzitil adj plus) or e-moxclav or enhancin or fleming or fugentin or (fullicilina adj plus) or gumentin or hibiotic or inciclav or klamonex or kmoxilin or lactamox or lansiclav or moxiclav or moxicle or moxyclav or natravox or nufaclav or palentin or quali-mentin or ranclav or spektramox or stacillin or suplentin or synermox or synulox or (velamox adj cl) or vestaclav or viaclav or vulamox or xiclav or (zami adj '8503')).ti,ab. (9184)

34 ((brl adj '17421') or brl17421 or (thiophenemalonamic adj acid) or negaban or temocillin or temopen).ti,ab. (179)

35 (tigecycline or (tbg adj mino) or tygacil or gar 936 or gar936 or (tert adj butylglycinamido$)).ab,ti. (1161)

36 exp Quinolones/ (33277)

37 ((chinolone adj derivative) or fluoroquinolones or (haloquinolone adj derivative) or ketoquinolines or oxoquinolines or quinolinones or quinolones).ti,ab. (11055)

38 exp Aminoglycosides/ (122582)

39 (Aminoglycosides or Anthracyclines or Aclarubicin or Daunorubicin or Plicamycin or Butirosin Sulfate or Sisomicin or Hygromycin B or Kanamycin or Dibekacin or Nebramycin + or Metrizamide or Neomycin or Framycetin or Paromomycin or Ribostamycin or Puromycin or Spectinomycin or Streptomycin or Dihydrostreptomycin Sulfate or Streptothricins or Streptozocin).ti,ab. (52288)

40 exp Gentamicins/ (16678)

41 (adelanin or alcomicin or apigent or apogen or apoten or azupel or bactiderm or biogaracin or bristagen or cidomycin or danigen or dermogen or dianfarma or dispagent or duragentam$ or epigent or (frieso adj gent) or garabiotic or garalone or garamicin$ or garamycin or garbilocin or gencin or gendril or genoptic or genrex or gensumycin or gentabiotic or gentabiox or gentac or gentacidin or gentacin or gentacor or gentacycol or gentacyl or gentafair or gentagram or gentak or gental or gentaline or gentalline or gentalol or gentalyn or gentamax or gentame$ or gentamicin$ or gentamina or gentamycin$ or gentamyl or gentamytrex or gentaplus or gentarad or gentasil or gentasol or gentasone or gentasporin or gentatrim or gentavet or genticin$ or genticyn or gentiderm or gentimycin or gentocin or gentogram or gentomycin or genum or geomycine or gevramycin or g-mycin or gmyticin or g-myticin or grammicin or hexamycin or jenamicin or konigen or lacromycin or lisagent or martigenta or migenta or miragenta or miramycin or nichogencin or nsc 82261 or nsc82261 or obogen or ocugenta or ocu-mycin or oftagen or ophtagram or opthagen or optigen or opti-genta or ottogenta or pyogenta or refobacin or ribomicin or rigaminol or rocy gen or rovixida or rupegen or sagestam or sch 9724 or sch9724 or sedanazin or servigenta or skinfect or sulmycin or tangyn or u-gencin or versigen or yectamicina).ti,ab. (19829)

42 exp Amikacin/ (3372)

43 (akacin or akicin or amicacina or amicasil or amicin or amiglymide v or amikacin$ or amikafur or amikalem or amikan or amikayect or amikin or amiklin or amikozit or amiktam or amitracin or amixin or amukin or apalin or bb k 8 or bb k8 or bbk 8 or bb-k 8 or bbk8 or bbk-8 or bb-k8 or biclin or biklin or biokacin or briclin or briklin or chemacin or cinmik or fabianol or gamikal or glukamin or kacinth-a or kanbine or kormakin or likacin or lukadin or miacin or mikasome or onikin or oprad or orlobin or pediakin or pierami or riklinak or savox or selaxa or selemycin or sulfate amikacin or tybikin or vs 107 or vs107 or yectamid).ti,ab. (7140)

44 exp Fosfomycin/ (1378)

45 (fosfocil or fosfocin or fosfocina or fosfomicin or fosfomycin or fosfonomycin or 'mk 0955' or mk 955 or mk0955 or mk955 or monuril or phosphomycin or phosphonomycin).ti,ab. (1779)

46 exp Aztreonam/ (1233)

47 ((az adj threonam) or azactam or azenam or azthreonam or aztreonam or (corus adj '1020') or dynabiotic or primbactam or SQ 26,776 or sq 26,776 or sq 26776 or SQ-26,776 or sq26776 or sq-26776 or urobactam).ti,ab. (2333)

48 exp Nitrofurantoin/ (2253)

49 (berkfurin or biofurin or chemiofuran or dantafur or f 30 or f30 or fua-med or furaben or furadantin$ or furadantoin or furadina or furadoine or furadonin or furadonine or furalan or furanpur or furantocompren or furantoin$ or furobactina or furofen or furophen or infurin or ituran or ivadantin or macrobid or macrodantin$ or macrofuran or macrofurin or micofurantin$ or mitrofuratoin or nephronex or nierofu or nifurantin or nifuryl or (nitro adj macro) or nitrofuracin or nitrofuradantoin or nitrofurantine or nitrofurantoin$ or nitrofurin or novofuran or nsc 2107 or nsc2107 or orafuran or parfuran or phenurin or (potassium adj furagin) or ralodantin or trocurine or urantin or (uro adj tablinen) or urodil or urodin or urofuran or urolong or urotablinen or uro-tablinen or urotoina or uvamin).ti,ab. (2721)

50 exp Cephalosporins/ (35352)

51 (Axepim$ or bmy 28142 or bmy28142 or BMY-28142 or Cefepim$ or cefepitax or ceficad or cepimax or forzyn beta or maxcef or maxfrom or maxipime or Quadrocef).ti,ab. (1916)

52 ((Cephalosporanic adj Acid$) or Cephalosporin$ or Cefamandole or Cefoperazone or Cefazolin or Cefonicid or Cefsulodin or Cephacetrile or Cefotaxime or Cephalothin or Cephapirin or Cephalexin or Cefaclor or Cefadroxil or Cephaloglycin or Cephradine or Cephaloridine or Ceftazidime or Cephamycins or Cefmetazole or Cefotetan or Cefoxitin).ti,ab. (35099)

53 exp Amdinocillin Pivoxil/ (199)

54 ((amdinocillin adj pivoxil) or (FL adj '1039') or FL1039 or fl1039 or FL-1039 or pivamdinocillin or Pivmecillinam or Selexid or coactabs or (ro adj '109071') or (ro10 adj '9071') or ro109071).ti,ab. (237)

55 or/25-54 (246506)

56 21 and 24 and 55 (3195)

57 exp clinical trial/ (706293)
58 exp randomized controlled trials/ (85563)
59 exp double-blind method/ (118498)
60 exp single-blind method/ (17086)
61 exp cross-over studies/ (30990)
62 randomized controlled trial.pt. (342334)
63 clinical trial.pt. (476450)
64 controlled clinical trial.pt. (85694)
65 (clinic$ adj2 trial).mp. (552367)
66 (random$ adj5 control$ adj5 trial$).mp. (443104)
67 (crossover or cross-over).mp. (59003)
68 ((singl$ or double$ or trebl$ or tripl$) adj (blind$ or mask$)).mp. (162179)
69 randomi$.mp. (509202)
70 (random$ adj5 (assign$ or allocat$ or assort$ or reciev$)).mp. (150717)
71 or/57-70 (968331)
72 (review or review,tutorial or review, academic).pt. (1758734)
73 (systematic$ adj5 review$).tw,sh. (40365)
74 (systematic$ adj5 overview$).tw,sh. (663)
75 (quantitativ$ adj5 review$).tw,sh. (3684)
76 (quantitativ$ adj5 overview$).tw,sh. (153)
77 (quantitativ$ adj5 synthesis$).tw,sh. (1107)
78 (methodologic$ adj5 review$).tw,sh. (2696)
79 (methodologic$ adj5 overview$).tw,sh. (180)
80 (integrative research review$ or research integration).tw. (78)
81 meta-analysis as topic/ (12608)
82 (meta-analys$ or meta analys$ or metaanalys$).tw,sh. (62359)
83 (meta synthesis or meta synthesis or metasynthesis).tw,sh. (215)
84 (meta-regression or meta regression or metaregression).tw,sh. (1650)
85 meta-analysis.pt. (37918)
86 (synthes$ adj3 literature).tw. (1070)
87 (synthes$ adj3 evidence).tw. (2956)
88 integrative review.tw. (583)
89 data synthesis.tw. (6328)
90 (research synthesis or narrative synthesis).tw. (463)
91 (systematic study or systematic studies).tw. (5679)

92 systematic comparison$.tw. (953)

93 systematic comparison$.tw. (953)

94 evidence based review.tw. (965)

95 comprehensive review$.tw. (5290)

96 critical review.tw. (9227)

97 quantitative review.tw. (382)

98 structured review.tw. (376)

99 realist review.tw. (24)

100 realist synthesis.tw. (11)

101 review.ti. (212126)

102 (review$ adj4 (papers or trials or studies or evidence or intervention$ or evaluation$)).tw. (80949)

103 metanaly$.tw. (137)

104 letter.pt. (766872)

105 editorial.pt. (310993)

106 comment.pt. (493546)

107 or/104-106 (1166749)

108 or/72-103 (1897061)

109 108 not 107 (1860495)

110 intervention?.ti. or (intervention? adj6 (clinician? or collaborat$ or community or complex or DESIGN$ or doctor? or educational or family doctor? or family physician? or family practitioner? or financial or GP or general practice? or hospital? or impact? or improv$ or individuali?e? or individuali?ing or interdisciplin$ or multicomponent or multi-component or multidisciplin$ or multi-disciplin$ or multifacet$ or multi-facet$ or multimodal$ or multi-modal$ or personali?e? or personali?ing or pharmacies or pharmacist? or pharmacy or physician? or practitioner? or prescrib$ or prescription? or primary care or professional$ or provider? or regulatory or regulatory or tailor$ or target$ or team$ or usual care)).ab. (128957)

111 (pre-intervention? or preintervention? or 'pre intervention?' or post-intervention? or postintervention? or 'post intervention?').ti,ab. (7451)

112 demonstration project?.ti,ab. (1742)

113 (pre-post or 'pre test$' or pretest$ or posttest$ or 'post test$' or (pre adj5 post)).ti,ab. (52427)

114 (pre-workshop or post-workshop or (before adj3 workshop) or (after adj3 workshop)).ti,ab. (472)

115 trial.ti. or ((study adj3 aim?) or 'our study').ab. (500725)

116 (before adj10 (after or during)).ti,ab. (314768)

117 ('quasi-experiment$' or quasiexperiment$ or 'quasi random$' or quasirandom$ or 'quasi control$' or quasicontrol$ or ((quasi$ or experimental) adj3 (method$ or study or trial or design$))).ti,ab,hw. (84783)

118 ('time series' adj2 interrupt$).ti,ab,hw. (744)

119 (time points adj3 (over or multiple or three or four or five or six or seven or eight or nine or ten or eleven or twelve or month$ or hour? or day? or 'more than')).ab. (7043)

120 pilot.ti. (32084)

121 Pilot projects/ (74648)

122 (clinical trial or controlled clinical trial or multicenter study).pt. (595489)

123 (multicentre or multicenter or multi-centre or multi-center).ti. (24301)

124 random$.ti,ab. or controlled.ti. (624993)

125 (control adj3 (area or cohort? or compare? or condition or design or group? or intervention? or participant? or study)).ab. not (controlled clinical trial or randomized controlled trial).pt. (342332)

126 'comment on'.cm. or review.ti,pt. or randomized controlled trial.pt. (2652864)

127 (rat or rats or cow or cows or chicken? or horse or horses or mice or mouse or bovine or animal?).ti. (1254855)

128 exp animals/ not humans.sh. (3812817)

129 (or/110-126) not (or/127-128) (3811646)

130 71 or 109 or 129 (4107075)

131 and 130 (822)

4.3.Clinical Review Tables

4.3.1. Antibiotic stewardship

	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Ben-David 2010 ITS **Setting** Tertiary (one hospital) Israel January 2006–December 2008	To assess the effect of an intensified intervention, that included active surveillance, on the incidence of infection with carbapenem-resistant *K. pneumoniae* **Participants** *N*=390 Age: not reported Male: not reported, female: not reported Inclusion criteria: data from medical records of all patients who acquired CRKP infection Exclusion criteria: not reported	**Bacteria**: *K. pneumoniae* **Resistant to**: carbapenems, cephalosporins, fluoroquinolones, trimethoprim-sulfamethoxazole **Mechanism of resistance**: not reported	**Intervention** 1. Enhanced national infection control programme: contact precautions were used for the care of all patients with CRKP colonization or infection; the prevalence of colonization or infection was reported daily, and this information was mailed to the hospital management and the national coordinator; and patients infected with CRKP had their names entered into a database so that they could be identified at hospital re-admission 2. Active surveillence programme: obtaining rectal culture samples from patients hospitalized in ICUs and in step-down units, at admission to the unit and once weekly until the patient was discharged **Length of pre-intervention**: 17 months prior **Length of post-intervention**: 19 months following	**Infection control** Before the intervention, the incidence of clinical infection with CRKP had increased 6.42-fold to 6.93 cases per 10,000 patient-days After an enhanced infection control and active surveillance programme was introduced, the incidence of clinical infection reduced to 1.8 cases per 10,000 patient-days (*P*<0.001). The slope significantly changed with the introduction of the intervention from 0.12 to -0.07 (*P*<0.001)	**ITS** **Protection against secular changes (high quality)** **Protection against detection bias (acceptable quality)**
Borer 2011 ITS	To devise a local strategy for eradication of a hospital-wide outbreak caused by CRKP	**Bacteria**: *K. pneumoniae*	**Intervention** 1. Emergency department flagging system	**Bacterial colonization and infection**	**ITS** **Protection against secular**

	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Setting Tertiary (one hospital) Israel May 2006–May 2010	**Participants** *N*=803 Adolescents 13–18 years, adults 19–45 years, middle aged 46–64 years, aged 65–79 years, elderly 80+years Male: 410, female: 393 Inclusion criteria: data from medical records of patients with CRKP infection Exclusion criteria: not reported	**Resistant to**: carbapenems **Mechanism of resistance**: not reported	2. Building of a cohort space or ward 3. Intensive active surveillance in high-risk wards 4. Epidemiological investigations 5. Carbapenem-restriction policy **Length of pre-intervention**: 11 months prior **Length of post-intervention**: 36 months following	During the intervention, the CRKP undetected ratio showed a significant increase from 55.7% for June–December 2007 to 71.2% in 2008, 78.9% in 2009 and 92.5% for February– May 2010 (*P*≤0.001). From May 2006 through April 2007 (pre-intervention), the CRKP-IN incidence density per 10,000 patient-days was 5.26. After the intervention programme was introduced, the incidence of clinical CRPK infection reduced to 2.91 cases per 10,000 patient-days (*P*<0.001) in 12/2007, 1.91 in 12/2008 and 1.28 in 12/2009. The slope changed significantly with the introduction of the intervention (*P*=0.004). **Antibiotic use** Meropenem use showed a statistically significant decrease from 2007 to 2010 (*P*≤0.001); colistin use increased significantly during the same period (*P*≤0.001)	**changes (high quality)** **Protection against detection bias (acceptable to low quality)**
Church 2011 ITS **Setting** Secondary (one hospital)	To assess the possible effects of varying usage of levofloxacin, gatifloxacin and moxifloxacin on *P. aeruginosa* susceptibility to piperacillin-tazobactam, cefepime and tobramycin **Participants** *N*: not reported	**Bacteria**: *P. aeruginosa* **Resistant to:** aminoglycosides (tobramycin), cephalosporins (cefepime), piperacillin/tazobactam	**Intervention** 1. Levofloxacin replaced with gatifloxacin in 2001 2. Gatifloxacin replaced with moxifloxacin in 2006 Ciprofloxacin available throughout study period	**Antibiotic resistance and susceptibility** No association between the susceptibility of *P. aeruginosa* isolates to tobramycin and formulary changes was noted. With cefepime, a significant change in susceptibility was detected after the introduction of gatifloxacin (*P*=0.0099) and	**ITS** Protection against secular changes (low quality) Protection against detectio bias (low quality

	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
USA January 2000-December 2008	Age: not reported Male: not reported, female: not reported Inclusion criteria: data from clinical microbiology and pharmacy databases of the Medical University of South Carolina Medical Centre Exclusion criteria: not reported	**Mechanism of resistance**: not reported	**Length of pre-intervention**: 15 months prior **Length of post-intervention 1**: 60 months **Length of post-intervention 2**: 30 months following	moxifloxacin (*P*=0.0571). In the case of piperacillin/tazobactam, a positive change in susceptibility over time was detected after introduction of moxifloxacin (*P*=0.0589). In each analysis, the effect of total fluoroquinolone usage was not significant	
Cohen 2011 ITS **Setting** Tertiary (one hospital) Israel March 2006–August 2010	To describe the implementation of an institution-wide, multiple-step intervention to curtail the epidemic spread of CRKP **Participants** *N*=33,570 Age: not reported Male: not reported, female: not reported Inclusion criteria: all patients affected by CRKP Exclusion criteria: not reported	**Bacteria**: *K. pneumoniae* **Resistant to**: carbapenems **Mechanism of resistance**: not reported	**Intervention** 1. Single-room isolation and contact precautions 2. Cohorting of patients and nursing staff, screening of patients in the same room as newly identified carriers of CRKP, and local protocol for continued cohorting of returning patients 3. Weekly active surveillance in the ICU 4. Active surveillance of patients on admission to the emergency department **Length of pre-intervention:** not reported **Length of post-intervention 1**: 14 months **Length of post-intervention 2**: 39 months **Length of post-intervention 3**: 2 years	**Bacterial colonization and infection** The incidence (total number of cases of in-hospital CRKP acquisition detected by clinical cultures) and weekly point prevalence were reported as the number of cases per 1000 hospital beds Incidence was found to change significantly after intervention 2 (06/2007) and 3 (10/2008). Prevalence was found to change significantly only in September 2009 (after intervention 4) In the emergency department, the mean rate of compliance with the active surveillance protocol (± SD) was 43% ± 10%	**ITS** **Protection against secular changes (high quality)** **Protection against detection bias (acceptable to low quality)**

	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
			Length of post-intervention 4: 15 months		
Dortch 2011 ITS **Setting** Tertiary (one TICU, one SICU) USA January 2001–December 2008	To examine the effect of the antibiotic stewardship programme on the incidence of resistant Gram-negative HAIs **Participants** SICU *N*=6044, TICU *N*=14,802 Adults 19–45 years, middle aged 46–64 years, aged 65–79 years Male: 14,277, female: 6569 Inclusion criteria: all patients admitted to the SICU or TICU during the study period who contracted an HAI with microbiological confirmation of at least one Gram-negative pathogen, at least 18 years of age Exclusion criteria: not reported	**Bacteria**: *P. aeruginosa, Acinetobacter* spp. **Resistant to**: aminoglycosides, carbapenems, cephalosporins (third- and fourth-generation), fluoroquinolones **Mechanism of resistance**: not reported	**Intervention** 1. Antibiotic stewardship: April 2002, guidelines for prophylactic antibiotics were devised for select procedures 2. Antibiotic rotation: January 2005, institution-wide initiative for surgical prophylaxis based on the Surgical Care Improvement Project **Length of pre-intervention**: 15 months **Length of post-intervention 1**: 11 months **Length of post-intervention 2**: 16 months	**Antibiotic use** Both in the SICU and TICU and there was a significant decrease in the utilization of total broad-spectrum antibiotics (BLIC, carbapenems, fluoroquinolones, third- and fourth-generation cephalosporins) targeting Gram-negative pathogens over the observation period (*P*<0.001) **Infection** During the 8-year observation period, the proportion of healthcare-associated infections caused by MDR Gram-negative pathogens decreased from 37.4% (2001) to 8.5% (2008), whereas the proportion of healthcare-associated infections caused by pan-sensitive pathogens increased from 34.1% to 53.2%	**ITS** **Protection against secular changes (high quality)** **Protection against detection bias (acceptable to low quality)**
Lewis 2012 ITS **Setting** Tertiary (11 ICUs and immediate care units) USA	To examine the effect of restricting ciprofloxacin use on the resistance of nosocomial Gram-negative bacilli, including *P. aeruginosa*, to group 2 carbapenems in a hospital's ICUs and intermediate care units **Participants** *N:* not reported Age: not reported	**Bacteria**: *E. aerogenes, E. cloacae, P. aeruginosa, A. baumannii* **Resistant to**: carbapenems (imipenem, meropenem, doripenem), cephalosporins	**Intervention** Restriction of ciprofloxacin: ciprofloxacin use was restricted hospital wide in July 2007; after this restriction, pre-approval by the on-call infectious diseases fellow was required for its use **Length of pre-intervention**: 42 months	**Antibiotic use** Following the restriction of ciprofloxacin, there was a significant decreasing trend (*P*=0.0027) in its use, from 87.09 DDD/1000 patient-days in 2004 to 8.04 DDD/1000 patient-days in 2010. Use of the group 2 carbapenems increased significantly (*P*=0.0134) from 11.96 DDD/1000 patient-days in 2004 to 28.19 DDD/1000 patient-days in	**ITS** **Protection against secular changes (high quality)** **Protection against detection bias (acceptable quality)**

	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
January 2004–December 2010	Male: not reported, female: not reported Inclusion criteria: all clinical ICU and intermediate care unit specimens (blood, sterile fluid, sputum, urine, wounds and anaerobic specimens) with test results that were positive for *P. aeruginosa, E. aerogenes, E. cloacae, A. baumannii* and *S. maltophilia*. Only nosocomial cases, defined as involving patients who had a hospital length of stay exceeding two days Exclusion criteria: results of surveillance and environmental sample cultures.	(cefepime), piperacillin/tazobactam, fluoroquinolones (ciprofloxacin) **Mechanism of resistance**: not reported	**Length of post-intervention**: 42 months	2010. Overall, there was a hospital-wide decrease of 18.4% (*P*<0.0001) in the use of antibacterials during the study time **Infection** There were no changes observed in the number of nosocomial *S. maltophilia* isolates per 10,000 patient-days following the restriction of ciprofloxacin **Antibiotic resistance** Over the seven-year time period, there was a decrease of 13.7% in the percentage of ciprofloxacin-resistant *P. aeruginosa* isolates that were collected, which equates to a decrease of 3.9% per year (*P*=0.0017). No significant changes was observed in the susceptibilities to the group II carbapenems of nosocomial Enterobacteriaceae or *A. baumannii* isolates	
Meyer 2009 ITS **Setting** Tertiary (one ICU) Germany January 2002–	To test whether reduction of third-generation cephalosporin use has a sustainable positive impact on the high endemic prevalence of third generation cephalosporin-resistant *K. pneumoniae* and *E. coli* in an ICU **Participants** *N*=3758 Age: not reported	**Bacteria**: *E. coli, K. pneumoniae, P. aeruginosa* **Resistant to**: cephalosporins (third-generation), piperacillin **Mechanism of resistance**: ESBL	**Intervention** 1. Education programmes for professionals and patients in July 2004 2. Education sessions on antibiotic guidelines were held in the departments of surgery and anaesthesiology 3. Empiric standard therapy for peritonitis and other intra-abominal infections was	**Antibiotic use** Following the implementation of guidelines in a surgical ICU, a significant and sustainable decrease in the use of third-generation cephalosporins of -110.2 DDD/1000 patient-days (95% CI -140.0 to -80.4, R^2=0.468) was observed. There was a significant reduction in the use of ampicillins (-167.4 DDD/1000, 95% CI -223.8 to -110.9, R^2=0.378) and in	**ITS** **Protection against secular changes (high quality)** **Protection against detection bias (high quality)**

	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
December 2006	Male: not reported, female: not reported Inclusion criteria: not reported Exclusion criteria: not reported		switched from third-generation cephalosporins to piperacillin in combination with a beta-lactamase inhibitor. The duration of antibiotic therapy for open fractures was shortened to single-shot pre-operative prophylaxis **Length of pre-intervention**: 30 months **Length of post-intervention**: 30 months	the use of imidazoles (-94.5 DDD/1000, 95% CI -121.2 to -67.7, R^2=0.463) The use of aminoglycosides decreased steadily before and after the intervention (slope -1.4 DDD/1000 patient-days per month, 95% CI -1.8 to -1.0, R^2=0.430); piperacillin and piperacillin/tazobactam showed a significant increase in level of 64.4 DDD/1000 patient-days (95% CI 38.5–90.3) and continued to increase by 2.3 DDD/1000 patient-days (95% CI 1.0–3.6) per month after the intervention (R^2=0.745)	
Meyer 2010 ITS **Setting** Tertiary (one ICU) Germany January 2002–December 2006	To evaluate the impact of a reduced duration of antibiotic prophylaxis for cerebrospinal shunts on total antibiotic use in the ICU and key resistant pathogens **Participants** *N*=11,887 Age: not reported Male: not reported, female: not reported Inclusion criteria: monthly data on antimicrobial use obtained from the computerized pharmacy database. Monthly resistance data collected from the microbiology laboratory.	**Bacteria**: *E. coli, K. pneumoniae, P. aeruginosa* **Resistant to**: carbapenems (imipenem), cephalosporins (third-generation) **Mechanism of resistance**: not reported	**Intervention** Change in antibiotic prophylaxis: Revised recommendation of single-shot prophylaxis with cefuroxime for shunt catheters, beginning in January 2004 **Length of pre-intervention**: 24 months prior **Length of post-intervention**: 36 months following	**Antibiotic use** Following the implementation of a comprehensive teaching session on antibiotic prophylaxis in cerebrospinal shunts in a surgical ICU, pre-operative prophylaxis for shunt catheters was changed into single-shot prophylaxis, and total antibiotic use decreased (–147.3 DDD/1000 patient-days, *P*=0.052). This corresponded to a decrease of 15% in the use of cefuroxime. The reduction in total antibiotic consumption was sustainable and did not increase over the next 36 months.	**ITS** **Protection against secular changes (high quality)** **Protection against detection bias (acceptable quality)**

	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
	Only samples taken in the ICU were considered Exclusion criteria: copy strains – defined as an isolate of the same species showing the same susceptibility pattern throughout a 1-month period in the same patient, no matter what the site of isolation				
Yong 2010 ITS **Setting** Tertiary (one ICU) Australia January 2000–December 2006	To perform an evaluation of changes in antibiotic susceptibility patterns in common Gram-negative organisms isolated from an ICU to demonstrate whether an observed reduction in broad-spectrum antibiotic use alters the resistance patterns of local bacteria **Participants** *N*=13,295 Age: not reported Male: not reported, female: not reported Inclusion criteria: not reported Exclusion criteria: not reported	**Bacteria**: *E. coli, Klebsiella* spp., *Enterobacter* spp., *P. aeruginosa, Acinetobacter* spp. **Resistant to**: aminoglycosides, carbapenems (imipenem), cephalosporins (ceftazidime), fluoroquinolones (ciprofloxacin) **Mechanism of resistance**: not reported	**Intervention** National guidelines on antimicrobial prescribing; antibiotic stewardship via computerized decision support systems. In 2001, one system guiding antibiotic use outside the ICU – a web-based antimicrobial approval system for third-generation cephalosporins (cefotaxime and ceftriaxone). In 2002, targeting the ICU specifically – computerized decision support system for antibiotic prescribing **Length of pre-intervention**: 30 months **Length of post-intervention**: 54 months	**Antibiotic use** Following the implementation of national guidelines on antimicrobial prescribing and antibiotic stewardship, there was a significant reduction in the number of imipenem-resistant *E. coli* and *Klebsiella* spp. isolates observed in the ICU. A small but significant improvement in the number of imipenem-resistant *Acinetobacter* spp. isolates was also observed. For Enterobacteriaceae with potentially inducible beta-lactamases, no significant changes was observed in imipenem susceptibility, although gentamicin susceptibility increased at a rate of 2.1%/year (95% CI 0.7–3.4), and ciprofloxacin susceptibility increased at a rate of 0.9%/year (95% CI 0.1–1.7) **ICU antibiotic consumption**	**ITS** **Protection against secular changes (high quality)** **Protection against detection bias (acceptable to low quality)**

	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
				The use of antibiotics to cover Gram-negative bacteria in the ICU, including third- and fourth-generation cephalosporins, carbapenems, extended-spectrum penicillins, aminoglycosides and fluoroquinolones remained stable during the study period	
Xue 2009 RCT **Setting** Tertiary (one ICU) China June 2007–December 2007	To determine the relation of carbapenem restriction with the incidence of MDR *A. baumannii* in VAP **Participants** *N*=26 Adults 19–45 years, middle aged 46–64 years, aged 65–79 years Male: 15, female: 11 Inclusion criteria: Patients receiving mechanical ventilation for more than five days and diagnosed with VAP Exclusion criteria: not reported	**Bacteria**: *A. baumanniii* **Resistant to**: carbapenems **Mechanism of resistance**: ESBL	**Intervention** Carbapenem restriction policy limiting the use of third-generation carbapenems. Only used when severe sepsis and after consultation with a physician from the Department of Infectious Diseases. *N*=12 **Control group** Conventional treatment: no restrictions of carbapenem (doctors were able to prescribe if necessary). *N*=15 **Length of follow-up**: duration of treatment	**Mortality** Mortality rates did not differ significantly between the treatment groups (RR 0.78; 95% CI 0.29–2.12). **Antibiotic resistance** More patients in the conventional group developed a carbapenem-resistant strain of *A. baumannii*, although the difference was not statistically significant (RR 0.63; 95% CI 0.38–1.04)	**RCT** Low methodological quality (0) Small sample size

K. pneumoniae, Klebsiella pneumonia; P.aeruginosa, Pseudomonas aeruginosa; A. baumanniii, Acinetobacter baumanniii; E. coli, Escherichia coli; E. aerogenes; Enterobacter aerogenes; E. cloacae, Enterobacter cloacae; S. maltophilia, *Stenotrophomonas maltophilia*; CRKP, carbapenem-resistant *K. pneumoniae*; SICU, surgical intensive care unit; TICU, trauma intensive care unit; VAP, ventilator-associated pneumonia; MDR, multi-drug resistant; ESBL, extended-spectrum beta-lactamase; BLIC, beta-lactam/beta-lactamase inhibitor combinations; ITS, interrupted time series; RCT, randomized controlled trial; ICU, intensive care unit; FQ, fluoroquinolones; 3/4CEPH, third- and fourth-generation cephalosporins; HAI, healthcare-associated infection; CI, confidence interval; RR, risk ratio; DDD, defined daily dose; SD, standard deviation.

4.3.2. Other infection control measures

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Levin 2010 CBA **Setting** Tertiary (two ICUs) Israel Dates not reported	To analyse whether single patient rooms in the ICU decreased bacterial transmission between ICU patients **Participants** *N*=207 Age: not reported Male: not reported, female: not reported Inclusion criteria: not reported Exclusion criteria: not reported	**Bacteria**: *Acinetobacter* spp., other Gram-negative bacteria **Resistant to**: carbapenems **Mechanism of resistance**: ESBL	**Intervention** ICU A converted to single patient rooms. Old ICU A *N*=64, new ICU A *N*=62 **Control group** ICU B remained open plan. Old ICU B *N*=44, new ICU B *N*=39 **Length of follow-up**: not reported	**Infection control** The single-room ICU A had a significantly lower ICU acquisition of resistant organisms when compared with ICU B during the same period [3/62 (5%) vs 7/39 (18%), respectively, *P*=0.043], which was confirmed using survival analysis (*P*=0.011). ICU B showed no changes over the study	**CBA** Low methodological quality (0)

ICU, intensive care unit; ESBL, extended-spectrum beta-lactamase; CBA, controlled before–after study.

4.3.3. Selective decontamination

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Agusti 2002 Quasi-randomized **Setting**	To determine the efficacy of SDD in patients with multi-drug-resistant *A. baumannii* intestinal colonization **Participants** *N*=54	**Bacteria**: *A. baumannii* **Resistant to**: aminoglycosides (tobramycine)	**Intervention** SDD: a combination of polymyxin E (colistin) (150 mg) and tobramycine (80 mg) administered in 20-mL liquid form x 4/day (orally or through	**Bacterial colonization** Rates of faecal, pharyngeal and axillary colonization did not significantly reduce during ICU stay in the control group (*P* value not reported). In the SDD group, the rate	**Quasi-randomized** Low methodological quality (0)

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Tertiary (one ICU) Spain October 1998–June 1999	Adults 19–45 years, middle aged 46–64 years, aged 65–79 years Male: 16, female: 5 Inclusion criteria: Intervention group 1. All patients with *A. baumannii* fecal colonization 2. An expected ICU stay exceeding five days Control group 1. All patients admitted 1 October–30 Novembe 1998 with *A. baumannii* faecal colonization 2. At least one series of axillary-pharyngeal-rectal swab performed Exclusion criteria: not reported	**Mechanism of resistance**: not reported	nasogastric tube), and 0.5 g of gel containing 2% of colistin and tobramycine applied round the gum margins and oropharynx x 4/day. Duration of treatment from detection of *A. baumannii* to discharge from ICU. *N*=21 **Control group** No intervention. *N*=33 **Length of follow-up**: duration of treatment	of faecal and pharyngeal carriage was reduced significantly (*P*<0.001 and *P*=0.003, respectively), but not the rate of cutaneous carriage **Antibiotic resistance** MDR *A. baumannii* had not been detected at the time of faecal carriage in 21 of 33 (63.6%) of the control group and 11 of 21 (52.3%) of the SDD group. In the SDD group, all *A. baumannii* strains were tobramycin resistant and susceptible to colistin at the beginning of the study. No resistance to colistin developed during the study	Small sample size
Brun-Buisson 1989 Quasi-randomized **Setting** Tertiary (one ICU) France January 1987-May 1987	To study the efficacy of intestinal decontamination by oral non-absorbable antibiotic agents to control a nosocomial outbreak of intestinal colonization and infection with MDR Enterobacteriaceae, and to examine its effects on endemic nosocomial infection rates. **Participants** *N*=86 Adults 19–45 years, middle aged 46–64 years, aged 65–79 years Male: not reported, female: not reported	**Bacteria**: *Enterobacter* spp., *P. aeruginosa* **Resistant to**: aminoglycosides (amikacin), third-generation cephalosporins **Mechanism of resistance**: ESBL	**Intervention** SDD: a combination of polymyxin E (colistin), 50 mg; neomycin, 1 g; and nalidixic acid (quinolone), 1 g administered in liquid form x 4/day either orally or through a nasogastric tube, starting within 24 h of admission and continuing until discharge from the unit. *N*=36 **Control group** No prophylaxis. *N*=50 **Length of follow-up**: not reported	**Mortality** All-cause mortality and mortality from nosocomial infections did not differ significantly between patients receiving SDD or no prophylaxis **Clinical success/improvement** There was no significant difference between patients receiving SDD or no prophylaxis in: – the incidence of any nosocomial infection – the infections caused by Gram-negative bacteria	**Quasi-randomized** Low methodological quality (0)

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
	Inclusion criteria: 1. Consecutive patients with unit stay exceeding two days 2. Severity score at admission >2 Exclusion criteria: 1. Severe neutropenia routinely receiving oral antibiotic prophylaxis			– the number of nosocomial infections that needed antibiotic treatment There was no significant difference in the number of patients staying on ICU longer than seven or 15 days **Bacterial colonization** One SDD patient and 12 no prophylaxis patients were positive for MDR strains (RR 0.12; 95% CI 0.02–0.85). No new cases of MDR strains of Enterobacteriacae were detected during the first four months after the trial **Adverse events** Three no prophylaxis patients needed therapy for a septic episode caused by Enterobacteriacae; however, this was not significantly different from the intervention group	
Saidel-Odes 2012 RCT **Setting** Tertiary (one internal medicine ward) Israel	To assess the effectiveness of SDD for eradicating CRKP oropharyngeal and gastrointestinal carriage **Participants** *N*=40 Middle aged 46–64 years, aged 65–79 years, elderly 80+ years Male: 26, female: 14 Inclusion criteria: 1. Hospitalized patients with CRKP colonization with or without infection	**Bacteria**: *K. pneumoniae* **Resistant to**: carbapenems **Mechanism of resistance**: not reported	**Intervention** SDD: topical application in the oropharynx of colistin sulfomethate sodium 100,000 U per g and gentamicin sulfate 1.6 mg per g incorporated into the gel. Dose of 0.5 g x 4/day for seven days. Plus an oral solution of 80 mg of gentamicin and 1x10 U of polymyxin E (colistin), given orally or through a nasogastric tube X 4/day for seven days. *N*=20	**Mortality** The rate of mortality did not differ significantly between the SDD group and the placebo group. The causes of mortality were not reported. No adverse events were reported **Antibiotic susceptibility** CRKP isolates from patients in the SDD arm remained susceptible to gentamicin and polymyxin E throughout the study (MIC ≤2 mg/mL and ≤0.094 mg/mL, respectively)	**RCT** High methodological quality (++) Small sample size

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
November 2008–June 2010	2. >18 years of age 3. Available for a follow-up period (while hospitalized or as outpatients) of at least seven weeks Exclusion criteria: <18 years of age, pregnancy, lactation, a known allergy to one of the study drugs, renal failure with creatinine clearance less than 50 mL/min, treatment with intravenous gentamicin or intravenous, polymyxin E at the time of randomization		**Control group** Placebo: topical application in the oropharynx of the placebo gel, which was compounded from carboxymethyl cellulose. Dose of 0.5 g x 4/day for seven days. Plus two oral solutions, one containing sodium chloride 0.45% and the other containing pulverized sacarin, given orally or through a nasogastric tube X 4/day for seven days. *N*=20 **Length of follow-up**: six weeks	**Bacterial colonization** At the end of treatment, the number of participants in the SDD group that had a throat culture that was CRKP positive reduced from 30% to 0%, whereas in the placebo group, this reduced from 35% to 30% (*P*<0.0001)	

A. baumannii, Acinetobacter baumannii; K. pneumoniae, Klebsiella pneumoniae; MDR, multi-drug resistant; SDD, selective digestive decontamination; RR, risk ratio, CI, confidence interval; CRKP, carbapenem-resistant *K. pneumonia*; MIC, minimum inhibitory concentration; RCT, randomized controlled trial; ICU, intensive care unit.

4.3.4. Systematic reviews

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Falagas 2009[1] **Setting** International Search up to January 2009	To assess the clinical and microbiological effectiveness of fosfomycin in the treatment of MDR, XDR or PDR non-fermenting Gram-negative bacterial infections **Participants** *N*=33 Studies: 23 microbiological, one animal and three cohort studies and three case reports Inclusion criteria: microbiological, animal experimental or clinical data on the effect of fosfomycin against MDR non-fermenting Gram-negative pathogens such as *Pseudomonas* spp., *Acinetobacter* spp., *Stenotrophomonas* spp. and *Burkholderia* spp. MDR, XDR or PDR non-fermenting Gram-negative bacilli or to Gram-negative bacilli with resistance to two or more classes of potentially effective antimicrobial agents Exclusion criteria: studies written in languages other than English, French, German, Italian or Spanish.	**Bacteria**: *Pseudomonas* spp., *Acinetobacter* spp., *Stenotrophomonas* spp. and *Burkholderia* spp. See Table II in the paper for details of clinical studies	**Intervention** Fosfomycin **Control group** Combination of fosfomycin with other antimicrobial agents	**Microbiological**: a total of 1859 MDR non-fermenting Gram-negative isolates. Susceptibility rate to fosfomycin of MDR *P. aeruginosa* isolates was ≥90% and 50–90% in 7/19 and 4/19 relevant studies, respectively. 30.2% isolates of MDR *P. aeruginosa*, 3.5% MDR *A. baumannii* isolates were found to be susceptible to fosfomycin **Clinical**: 91% of the patients clinically improved (treatment of infections caused by MDR *P. aeruginosa*)	Low methodological quality (0) This review was included because it is on the topic; however, the conclusions reached are not supported by the study design

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
	Studies representing abstracts in scientific conferences				
Falagas 2009[2] **Setting** Not reported Searches performed: 9 July 2008, 16 July 2008 and 11 September 2008	To evaluate the available clinical evidence regarding the effectiveness and safety of systemic colistin in children without cystic fibrosis **Participants** *N*=370 Studies: 10 case series and 15 case reports Inclusion criteria: studies with data regarding the use of intravenous, intrathecal, intramuscular or intraventricular colistin in paediatric patients for the treatment of infections caused by colistin-susceptible pathogens or for prophylaxis. All or the majority of patients involved in each individual study should not have cystic fibrosis Exclusion criteria: studies that focused on colistin use in paediatric patients with cystic fibrosis, or reporting the use of oral colistin or the use of colistin for topical treatment in paediatric patients. Abstracts in scientific conferences or studies published in languages other than English, Spanish, French, German, Italian or Greek	**Bacteria***: P. aeruginosa, A. baumannii, K. aerogenes, H. influenza, P. pyocyanin, P. aeruginosa, K. pneumoniae* and *A. aerogenes* See Table I in the paper for details of studies	**Intervention** Colistin for the treatment of infections (*N*=326) **Control group** Colistin for surgical prophylaxis or prophylaxis of infections in burns patients (*N*=44)	**Case series treatment:** 271 evaluable subjects Cure: 235/271 Improvement: 10/271 Deterioration: 6/271 Death: 20/271 Adverse effects (included in safety assessment *N*=311) 1. Nephrotoxicity: 33/311 had cylindruria or haematuria, 8/311 had a blood urea nitrogen elevation of >10% (in one child owing to an overdosage of colistin), 5/311 had renal tubular cells in the urine, 3/311 had proteinuria and 2/311 had a significant increase in serum creatinine levels during intravenous colistin treatment. Data regarding adverse events not provided for two children 2. Neurotoxicity: 0/311 3. Other: 8/311 **Case series prophylaxis:** Incidence of infection: 0/44 Death: 9/44 attributed to the underlying pathologies. No signs of colistin-related toxicity were found Adverse effects: 1. Tubular epithelial cells in urine, persistent for up	Acceptable methodological quality (+) This review was included because it is on the topic; however, the conclusions reached are not supported by the study design

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
				to one week after withdrawal of colistin: 16/44 2. Proteinuria, disappearing right after colistin withdrawal: 14/44 3. Oliguria during the initial stages of colistin treatment: 1/44 4. No adverse events: 13/44	
Falagas 2010[3] **Setting** International Searches up to January 2009	To the evidence on fosfomycin as a treatment option for infections caused by members of the family Enterobacteriaceae with advanced resistance to antimicrobial drugs, including producers of ESBL **Participants** *N*=119 Studies: 17 in-vitro microbiological studies, two prospective studies, one retrospective study and two case reports Inclusion criteria: studies on Enterobacteriaceae isolates with an advanced drug resistance (MDR, carbapenem resistance, or production of ESBLs, AmpC β-lactamases, serine carbapenemases or metallo-β-lactamases) profile and their susceptibility to fosfomycin, and the clinical effectiveness of treatment with fosfomycin for infections with these pathogens	**Bacteria***:* **Microbiological studies** *K. pneumoniae isolates, E. coli* **Clinical studies** *E. coli, S. typhimurium, S. typhi* See Table III in the paper for details of studies	**Intervention** Amoxicillin-clavulanate potassium **Control group** Fosfomycin–trometamol in two of the *E. coli* studies	**Microbiological success** 11 of the 17 studies reported that at least 90% of the isolates were susceptible to fosfomycin **Clinical efficacy** Measured in four studies. Two studies oral treatment for lower UTI with ESBL-producing *E. coli* (one prospective and one retrospective) resulted in the treatment group with clinical cure in 75 of the 80 (93.8%) patients included in these studies. Two case reports of infection due to MDR *Salmonella* spp. Reported treatment was effective with fosfomycin	Low methodological quality (0) This review was included because it is on the topic; however, the conclusions reached are not supported by the study design

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
	Exclusion criteria: abstracts in scientific conferences or studies published in languages other than English, Spanish, French, German, Italian or Greek				
Falagas 2012[4] **Setting** Not reported Searches from 2000 to 2010	To identify and evaluate the available data regarding the susceptibility of recent Gram-negative bacteria to isepamicin, including that of MDR strains of bacteria **Participants** *N*=512 Studies=11 microbiological, one RCT, one prospective study, one restrospective study Inclusion criteria: either a microbiological (in-vitro) study that evaluated the susceptibility of Gram-negative bacterial isolates (including MDR ones) to isepamicin or a clinical study that evaluated the use of isepamicin, given for the treatment of infections by the aforementioned pathogens or for prophylaxis for this type of infection. In addition, studies deemed relevant should have been published between 2000 and 2010 Exclusion criteria: studies that examined a sample of fewer than 10	**Bacteria:** **Clinical studies** *S. epidermidis, E. coli, S. pneumoniae, P. aeruginosa* See Table II in the paper for details of studies	**Intervention** Isepamicin **Control group** Two clinical studies – amikacin one clinical study – isepamicin + levofloxacin for prophylaxis	**Microbiological:** isepamicin was more effective in four studies than amikacin, six studies reported as effective, one study both groups ineffective. In studies including MDR bacteria, 2/4 reported more effective than amikacin; 1/4 as effective as amikacin; 1/4 both isepamicin and amikacin ineffective **Clinical:** 1. Paediatric infection treatment studies: 100% clinical and bacteriological response for both the isepamicin and the amikacin arms. Definition of clinical response not stated (e.g. cure, improvement) 2. Prophylactic study: acute bacterial prostatitis 1.3%	Low methodological quality (0) This review was included because it is on the topic; however, the conclusions reached are not supported by the study design

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
	isolates or patients, studies referring to synergistic or pharmacodynamic/ pharmacokinetic parameters of isepamicin, studies that provided data regarding the susceptibility of isepamicin to micro-organisms other than Gram-negative bacteria or the susceptibility of other aminoglycosides only to Gram-negative bacteria. Abstracts in scientific conferences or studies published in languages other than English, Spanish, French, German or Italian				
Kaki 2011[5] **Setting** International Search January 1996 to December 2010	To evaluate the current state of evidence for antimicrobial stewardship interventions in the critical care unit **Participants** *N*=not available/not reported for all included studies Studies: three RCTs, three ITSs, and 18 uncontrolled before–after studies Inclusion criteria: application of any intervention; to improve antimicrobial utilization; and within an intensive care setting Exclusion criteria: if no intervention was applied, non-human or non-patient based, non-hospital based, or they did not involve intensive care	**Bacteria:** *P. aeruginosa,* *A. baumannii,* *E. coli,* *Klebsiella* spp., ESBL See Table I in the paper for details of studies.	**Intervention** Antimicrobial stewardship: 1. Antibiotic restriction/ pre-approval 2. Computer-assisted decision support 3. Infectious diseases consultant 4. Re-assessment on pre-specified date 5. Antibiotic de-escalation protocols 6. Antibiotic prophylaxis guideline 7. Antibiotic treatment guideline **Control group** Not reported, presumably no stewardship	Overall stewardship intervention: 1. Reductions in antimicrobial utilization (11–38% defined daily dose/1000 patient-days) 2. Lower total antimicrobial costs (US$ 5–10/ patient-day) 3. Shorter average duration of antibiotic therapy 4. Less inappropriate use 5. Fewer antibiotic adverse events. stewardship intervention beyond six months: 1. Reductions in antimicrobial resistance rates Antibiotic stewardship was not associated with increases in nosocomial infection rates, length of stay or mortality	High methodological quality (++)

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
	patients. Additionally, antibiotic cycling. Conference abstracts				
Siempos 2007[6] **Setting** Not reported Search January 1950 to March 2006	To clarify whether carbapenems are more effective or safer than other broad-spectrum antibiotics for the empirical treatment of patients with HAP **Participants** *N*=2731 Studies: 12 RCTs Inclusion criteria: randomized controlled clinical trial; studied the role of carbapenems in comparison with other broad-spectrum antibiotics or a combination of antibiotics for the empirical treatment of patients with HAP; assessed the effectiveness, toxicity and mortality of both therapeutic regimens. Included both patients with HAP and patients with community-acquired pneumonia; however, only data regarding patients with HAP were extracted. Trials with both blind and unblind design were included, and only RCTs written in English, French and German Exclusion criteria: RCTs conducted primarily in neutropenic patients with solid organ tumours or	**Bacteria:** *P. aeruginosa* See Table I in the paper for details of studies	**Intervention** Carbapenems: 1. Imipenem/ cilastatin (eight studies) 2. Meropenem (four studies) **Control group** Imipenem/ cilastatin compared with: 1. Fluoroquinolones: levofloxacin, ciprofloxacin (three studies) 2. Other beta-lactams: piperacillin/tazobactam, aztreonam, cefepime, ceftazidime (five studies) Meropenem compared with: combination of a cephalosporin (ceftazidime, cefuroxime) with an aminoglycoside (amikacin, gentamicin, tobramycin)	1. All-cause mortality: lower mortality in the carbapenems group (OR 0.72, 95% CI 0.55–0.95) 2. Treatment success (clinical): no difference between groups (OR 1.08, 95% CI 0.91–1.29) 3. Treatment success (microbiological): no difference between groups (OR 1.04, 95% CI 0.72–1.50) 4. Adverse effects: no difference (0.81, 0.46–1.43) *P. aeruginosa* pneumonia subgroup: lower treatment success (OR 0.42, 95% CI 0.22–0.82) and lower eradication of *Pseudomonas* spp. strains (OR 0.50, 95% CI 0.24–0.89) in the carbamenems group. Late onset of HAP subgroup: no difference between groups (OR 1.34, 95% CI 0.91–1.97)	High methodological quality (++)

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
	haematological malignancies and trials that included fewer than 10 patients with pneumonia who received a carbapenem. Experimental trials and trials focusing on pharmacokinetic and pharmacodynamics parameters. Finally, RCTs comparing the effectiveness and safety of two different carbapenems				

P. aeruginosa, Pseudomonas aeruginosa; A. baumannii, Acinetobacter baumannii; K. aerogenes, Klebsiella aerogenes; H. influenza, Haemophilus influenza; P. pyocyanin, Pseudomonas pyocyanin; K. pneumoniae, Klebsiella pneumoniae; A. aerogenes, Aerobacter aerogenes; E. coli; Escherichia coli; S. typhimurium, *Salmonella typhimurium*;*S.typhi, Salmonella typhi; S. pneumoniae, Streptococcus pneumoniae; S. epidermidis, Staphylococcus epidermidis;* MDR, multi-drug resistant; XDR, extensively drug resistant; PDR, pan-drug resistant; RCT, randomized controlled trial; ESBL, extended-spectrum beta-lactamase; HAP, hospital-acquired pneumonia; OR, odds ratio; CI, confidence interval.

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4.3.5. Treatment

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Betrosian 2007 RCT **Setting** Tertiary (1 ICU) Greece October 2004–February 2006	To evaluate the clinical efficacy and safety of high-dose regimen ampicillin sulbactam for the treatment of VAP from MDR *A. baumannii* **Participants** *N*=27 Age: not reported Male: 15, female: *N*=12 Inclusion criteria: all patients mechanically ventilated for more than 72 h with positive tracheal aspirates for *A. baumannii* Exclusion criteria: episodes of VAP in which *A. baumannii* was isolated in conjunction with another micro-organism	**Bacteria**: *A. baumannii* **Resistant to**: ampicillin/sulbactam and susceptible exclusively to colistin (polymyxin E) **Mechanism of resistance**: not reported	**Intervention** Ampicillin/sulbactam at a rate 2: 1 every 8 h. 24 g/12 g daily for seven to 10 days. *N*=13 **Control group** Ampicillin/sulbactam at a rate 2: 1 every 8 h. 18 g/9 g daily for seven to 10 days. *N*=14 **Length of follow-up**: one month	**Mortality** 14-day VAP mortality and 30-day all-cause mortality were not significantly different between treatment groups **Clinical success/improvement** The number of patients with clinical success and clinical failure was not significantly different between treatment groups **Bacterial colonization** The two treatment groups showed no difference in the eradication of *A. baumannii* isolates (bacteriological success), bacteriological failure or superinfection **Adverse events** There was no difference in the adverse effects experienced by participants	**RCT** Low methodological quality (0) Very small sample size
Betrosian 2008 RCT	To compare the clinical efficacy and safety of high-dose ampicillin/sulbactam vs colistin as monotherapy for the treatment of *Acinetobacter* spp. VAP	**Bacteria**: *A. baumannii* **Resistant to**: Aminoglycosides, carbapenems,	**Intervention** Colistin, intravenous 3 MIU every 8 h for eight to 10 days. *N*=15	**Mortality** 14-day VAP mortality and 28-day all-cause mortality were not significantly different between treatment groups	**RCT** Low methodological quality (0)

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Setting Tertiary (2 ICUs) Greece Dates not reported	**Participants** *N*=28 Middle aged 46–64 years, aged 65–79 years Male: 14, female: 14 Inclusion criteria: ventilated patients for >72 h who developed MDR *A. baumannii* VAP Exclusion criteria: cases of VAP with mixed isolated micro-organisms, combination antibiotic therapy, allergy to beta-lactamase or penicillin, or previous enrolment in similar studies	cephalosporins, fluoroquinolones **Mechanism of resistance**: not reported	**Control group** Ampicillin/sulbactam, 9 g (at a rate 2:1) every 8 h for eight to 10 days, administered as follows: three vials (20 mL each) containing 3.0 g of ampicillin/sulbactam diluted in 200 mL of 5% dextrose provided within 1-h duration infusion. *N*=13 **Length of follow-up**: two-week- and one-month mortalities	**Clinical success/improvement** The number of patients with clinical success and clinical failure was not significantly different between treatment groups **Bacterial colonization** The two treatment groups showed no difference in the eradication of *A. baumannii* isolates (bacteriological success) or bacteriological failure (persistence of *A. baumannii* isolates (>104 CFU/mL) **Adverse events** There was no difference in the adverse effects experienced by participants	Small sample size
Chastre 2003 RCT **Setting** Tertiary (51 ICUs) France May 1999-June 2002	To compare the efficacy of eight days vs 15 days of antibiotic treatment of patients with microbiologically proven VAP **Participants** *N*=401 Middle aged 46–64 years, aged 65–79 years Male: 141, female: 46 Inclusion criteria: 1. >18 years of age 2. Clinical suspicion of VAP 3. Positive quantitative cultures of distal pulmonary secretion samples	**Bacteria**: *E. coli, Klebsiella* spp., *Enterobacter* spp., *P. aeruginosa, Acinetobacter* spp., *Proteus spp., Serratia spp., C. freundii, M. morgagnii* **Resistant to**: ticarcillin, methicillin **Mechanism of resistance**: ESBL	**Intervention** Antibiotics for eight days: specific antibiotics, doses and schedules are not reported. Antibiotics were selected by the treating physicians. As per protocol, the initial regimen should have preferably combined at least an aminoglycoside, or a fluoroquinolone and a broad-spectrum beta-lactam antimicribial agent. *N*=197 **Control group**	**Mortality** 28-day and 60-day all-cause mortality and in-hospital mortality did not significantly differ between the eight- and 15-day regimes **Clinical success/improvement** Risk differences (90% CIs) to develop an unfavourable outcome (defined as death, pulmonary infection recurrence, or prescription of a new antibiotic for any reason provided for ≥48 h) were not significantly different between the eight- and 15-day regimes for all patients (RR 2.6, 90% CI -5.6 to 10.7) and for those patients with	**RCT** High methodological quality (++)

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
	4. Instigation within the 24 h following of appropriate empirical antibiotic therapy directed against the micro-organism/s responsible for the infection Exclusion criteria: 1. Pregnant 2. Enrolled in another trial 3. Little chance of survival 4. Neutropenia 5. Concomitant acquired immunodiffeciency syndrome 6. Immunosuppressants or long-term corticosteroid therapy 7. Concomitant extrapulmonary infection that required prolonged antimicrobial treatment 8. Attending physical declined full-life support. 9. Early-onset pneumonia (within the first five days of mechanical ventilation) and no antimicrobial therapy during the 15 days preceding infection.		Antibiotics for 15 days: specific antibiotics, doses and schedules are not reported. Antibiotics were selected by the treating physicians. As per protocol, the initial regimen should have preferably combined at least an aminoglycoside or a fluoroquinolone and a broad-spectrum beta-lactam antimicribial agent. *N*=204 **Length of follow-up**: three months	non-fermenting Gram-negative bacteria (RR 8.6, 90% CI -5.9 to 23.1) The rate of and time to (Kaplan-Meier method, log-rank test) pulmonary infection considered to be recurrence, relapses or superinfection was not significantly different between treatment regimes. **Antibiotic use** The number of antibiotic-free days was significantly less for all patients on the eight-day regime, but not for those patients with non-fermenting Gram-negative bacteria. No difference was found in the number of patients continuing to receive antibiotics after the end of the trial treatment regimen, or in the number of patients who received an additional course of antibiotics **Antibiotic resistance** For patients who developed recurrent pulmonary infections, those who had received the eight-day treatment of antibiotics had significantly less emergence of MDR pathogens compared with those who had received the 15-day treatment (42.1% vs 62.3% of recurrent infections, respectively; *P*=0.04)	

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Cox 1987 RCT **Setting** Secondary (two hospitals) USA March 1985–December 1985	To compare the efficacy of norfloxacin vs standard parenteral treatment of non-bacteraemic, hospital-acquired UTI **Participants** *N*=104 Age: not reported Male: not reported, female: not reported Inclusion criteria: 1. Hospitalized patients 2. >18 years of age 3. Documented UTI caused by an organism known or presumed susceptible to norfloxacin Exclusion criteria: 1. <18 years of age 2. Pregnant or not practising an effective means of birth control 3. A history of allergic diathesis or an allergy to nalidixic acid, oxolinic acid or norfloxacin 4. Functional renal abnormalities or unstable deteriorating renal function 5. Comatose or high probability of imminent death 6. Serious concurrent infection 7. Treated or recently completed treatment with antibiotics 8. History or visual disturbances, a psychiatric disorder or central nervous system disease	**Bacteria**: *E. coli, Klebsiella* spp., *Enterobacter* spp., *P. aeruginosa, Serratia* spp., *C. freundii, M. morgagnii* **Resistant to**: not reported **Mechanism of resistance**: not reported	**Intervention** Norfloxacin 400 mg x2/day, minimum treatment seven days. *N*=52 (46 evaluable patients) **Control group** Aminoglycosides alone; aminoglycosides and meziocillin/ticarcillin; aminoglycosides and cephalosporin; aminoglycosides and vancomycin, cephalosporin, cefotaxime alone, administered in accordance with the manufacturers' guidelines. *N*=52 (48 evaluable patients) **Length of follow-up**: seven (SD two) days, optional four to six weeks	**Clinical success/improvement** No significant differences were found between norfloxacin and standard parenteral antibiotic treatment in the rate of participants that were clinically cured, showed clinical improvement or had treatment failure **Superinfection** Rates of superinfection and early re-infection also did not differ significantly between the norfloxacin and standard parenteral antibiotic treatment groups **Antibiotic resistance** No differences in the number of patients experiencing adverse events were found between those receiving norfloxacin and those receiving standard parenteral antibiotics	**RCT** Acceptable methodological quality (+)

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Giamarellou 1990 RCT **Setting** Tertiary (one ICU) Greece Dates not reported	To evaluate the efficacy of monotherapy with pefloxacin in secondary ICU pulmonary infections in comparison with imipenem **Participants** *N*=71 Adults 19–45 years, middle aged 46–64 years, aged 65–79 years, elderly 80+ years Male: 42, female: 29 Inclusion criteria: adult patients presenting serious bacterial infections of the respiratory tract Exclusion criteria: not reported	**Bacteria**: *E. coli, K. pneumoniae, Enterobacter* spp. (various Enterobacteriaceae), *P. aeruginosa, A. anitratus, P. mira, S. marcescens* **Resistant to**: aminoglycosides (gentamicine, tobramycin, netilmicin, amikacin), aztreonam, carbapenems (imipenem), cephalosporins (cefotaxime, ceftazidime, ceftriaxone), fluoroquinolones (ciprofloxacin) **Mechanism of resistance**: not reported	**Intervention** Pefloxacin intravenously 400 mg, every 8 h for 11.5 (SD 5.8) days. *N*=35 **Control group** Imipenem intravenously 1 g every 8 h for 12.9 (SD 6.2) days. *N*=36 **Length of follow-up**: duration of treatment	**Mortality** There were three deaths related to sepsis in the imipenem group and one in the pefloxacin group (although the sepsis was not related to the bronchopneumonia, but to an underlying abdominal infection). All-cause mortality was not reported **Clinical success/improvement** No differences were found in the number of patients cured, the number with superinfection that was cured, the number showing improvement and the number experiencing treatment failure. Bacterial eradication rates were significantly lower in the imipemem group [55.3% vs 82.9%, respectively (*P*<0.001)] **Antibiotic resistance** Resistance development among persisting strains was also significantly different (data not reported, *P*<0.05) **Adverse events** No systemic reactions or abnormal laboratory parameters were reported in either treatment group	**RCT** Acceptable methodological quality (+)
Huttner 2013	To investigate if intestinal carriage of ESBL-E can be eradicated	**Bacteria**: *Enterobacter* spp. (ESBL-E)	**Intervention** Colistin sulfate 50 mg (equivalent to 42 mg colistin	**Clinical success/improvement** The rate of eradication of ESBL-E was significantly different between	**RCT**

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
RCT **Setting** Secondary (all inpatient wards of a single hospital) Switzerland June 2009–June 2012	**Participants** *N*=58 Adolescents 13–18 years, adults 19–45 years, middle aged 46–64 years, aged 65–79 years, elderly 80+ years Male: 34, female: 24 Inclusion criteria: aged ≥18 years; ESLB-E-positive rectal swab Exclusion criteria: patients with active ESLB infection, patients treated with antibiotics active against ESLB-E, pregnancy/breastfeeding, contraindication to the use of study drugs, previous study enrolment and resistance of the colonizing ESLB-E strain to colistin (defined as MIC >2 mg/L	**Resistant to**: cefotaxime, cefotaxime/clavulanic acid, ceftazidime, ceftazidime/clavulanic acid, cefepime, cefepime/clavulanic acid **Mechanism of resistance**: ESBL	base or 1.26 million units 4x/day) and neomycin sulfate (250 mg equivalent to 178 mg neomycin base 4xday) for 10 days. In the presence of ESBL-E bacteriuria, the patients were also treated with nitrofurantoin (100 mg 3x/day) for five days. *N*=27 **Control group** Placebo. *N*=27 **Length of follow-up**: 28 (SD seven) days	treatment regimes during treatment (day 6; RR 0.40; 95% CI 0.23–0.70) or in the first day after treatment (RR 0.42; 95% CI 0.23–0.76), but did not differ in the end of follow-up **Treatment adherence** There was no significant difference between groups in the number of patients that adhered to treatment, measured by counting the number of pills on the boxes of study medication **Adverse events** No statistically significant difference was found between the treatment groups in the number of patients with at least one episode of liquid stool	High methodological quality (++)
Moskowitz 2011 RCT **Setting** Secondary (seven cystic fibrosis centres) USA February 2007–	To assess whether biofilm-growing bacteria susceptibility testing of *P. aeruginosa* correlates better with clinical outcomes in chronic cystic fibrosis airway infections, when compared with conventional antibiotic susceptibility testing **Participants** *N*=39 Adolescents 13–18 years, adults 19–45 years Male: 25, female: 14	**Bacteria**: *P. aeruginosa* **Resistant to**: aminoglycosides, fluoroquinolones **Mechanism of resistance**: not reported	**Intervention** Biofilm testing: bioflim regimens of two antibiotics were selected centrally using a published algorithm, which calculated for each bacterial morphotype the biofilm minimum inhibitory quotient of each drug, defined as achievable serum concentration divided by biofilm MIC. *N*=20 **Control group** Conventional testing: conventional regimens of two	**Antibiotic susceptibility** Participants were assigned to 12 different regimens. The most common regimens included meropenem (52%) and ciprofloxacin (49%). Azithromycin-containing regimens were used for only two participants (5%), both in the biofilm group. No participant received ceftazidime and tobramycin, a combination commonly used in cystic fibrosis clinical practice	**RCT** Acceptable methodological quality (+) Small sample size

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
October 2007	Inclusion criteria: diagnosis of cystic fibrosis, history of persistent *P. aeruginosa* airway infection, clinical stability at the time of screening, ≥14 years with at least one prior course of intravenous antibiotics Exclusion criteria: sputum culture negative for *P. aeruginosa*, sputum culture positive for *B. cepacia* complex species, hospitalization or treatment for an acute pulmonary exacerbation, treatment with oral or inhaled antipseudomonal antibiotics, or azithromycin or other macrolides, within 14 days prior to screening		antibiotics were selected centrally using a published algorithm, which calculated for each bacterial morphotype the conventional minimum inhibitory quotient of each drug defined as achievable serum concentration divided by conventional MIC. *N*=19 **Length of follow-up**: 14 days	Of the agents tested, meropenem was most active against biofilm-grown bacteria, but antibiotic regimens based on biofilm testing did not differ significantly from regimens based on conventional testing in terms of microbiological and clinical responses	
Rattanaumpawan 2010 RCT **Setting** Tertiary (one hospital) Thailand July 2006–September 2009	To determine whether nebulized CMS as adjunctive therapy of Gram-negative VAP was safe and beneficial **Participants** *N*=100 Middle aged 46–64 years, aged 65–79 years, elderly 80+ years Male: 64, female: 36 Inclusion criteria: hospitalized patients, ≥18 years of age, diagnosis of Gram-negative VAP Exclusion criteria: not reported	**Bacteria**: *E. coli* (ESBL +ve) and *E. coli* (ESBL -ve), *K. pneumoniae* (ESBL +ve) and *K. pneumoniae* (ESBL -ve), *E. cloacae, P. aeruginosa, A. baumannii* **Resistant to**: aminoglycosides, carbapenems, fluoroquinolones **Mechanism of resistance**: ESBL	**Intervention** Systemic antibiotic and nebulized CMS (parenteral) equivalent to 75 mg of colistin base reconstituted in 4 mL of NSS every 12 h via a nebulizer for 10 min. Continued until systemic antibiotic therapy of VAP was ended (decided by physician). *N*=51 **Control group** Systemic antibiotic(s) plus NSS equivalent to 75 mg of colistin base reconstituted in 4 mL of NSS every 12 h via a nebulizer for 10 min. Continued until systemic antibiotic therapy of VAP was ended. *N*=49	**Mortality** Rates of mortality due to VAP and all-cause mortality did not differ between the groups receiving intervention or control **Clinical success/improvement** Favourable microbiological outcome was significantly higher in the intervention group compared with the control group (RR 1.57, 95% CI 1.03–2.37),but no significant difference was observed on clinical outcomes The overall incidence of complications, bronchospasm and renal impairment did not differ between the two treatment groups	**RCT** Acceptable methodological quality (+)

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
			Length of follow-up: 28 days		
Stenderup 1983 RCT **Setting** Community Denmark Dates not reported	To study the use of mecillinam as a prophylactic for travellers' diarrhoea **Participants** *N*=74 tourists Adults 19–45 years, middle aged 46–64 years, aged 65–79 years, elderly 80+ years Male: not reported, female: not reported Inclusion criteria: Danish tourists travelling to Egypt and the Far East Exclusion criteria: not reported	**Bacteria**: Enterotoxogeni *E. coli* **Resistant to**: mecillinam, tetracyline, sulfonamide, streptomycin, chloramphenicol, kanamycin, ampicillin, cephalosporin, carbenicillin **Mechanism of resistance**: not reported	**Intervention** Mecillincam, 200 g, 1x per day for 25 days. *N*=38 **Control group** Placebo. *N*=36 **Length of follow-up**: duration of treatment	**Antibiotic resistance** Only 8% of *E. coli* strains were resistant to three or more antibiotics in the pre-travel samples. Post-travel, after participants had received either mecillinam or placebo, approximately 50% or more of the *E. coli* was resistant to more than three antibiotics	**RCT** Low methodological quality (0)
Tannock 2011 RCT **Setting** Primary (14 long-term care facilities) New Zealand Dates not reported	To test the efficacy of probiotic strain *E. coli* Nissle 1917 in reducing the carriage of MDR *E. coli* **Participants** *N*=70 Age: not reported Male: not reported, female: not reported Inclusion criteria: not reported Exclusion criteria: not reported	**Bacteria**: *E. coli* **Resistant to**: fluoroquinolones (norfloxacin) **Mechanism of resistance**: ESBL	**Intervention** Probiotic: strain *E. coli* Nissle 1917, $5x10^9$-$5x10^{10}$ CFU one capsule twice daily for five weeks. *N*=36 **Control group** Placebo starch powder capsule. *N*=33 **Length of follow-up**: five weeks	**Clinical success/improvement** There was no significant difference between the probiotic and placebo groups in the number of people with faecal and urine samples becoming negative or remaining positive. **Antibiotic resistance** 103 norfloxacin-resistant *E. coli* isolates from 20 probiotic patients were tested for susceptibility. All isolates were resistant to norfloxacin (MIC >256 µg/mL) and ciprofloxacin. The majority of norfloxacin-resistant *E. coli* isolates were MDR. The combination of MDRs differed	**RCT** Acceptable methodological quality (+)

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
				among strains. None of the isolates were ESBL producers.	
Wang 2009 RCT **Setting** Tertiary (one ICU) China March 2006–July 2006	To report the effectiveness of extended-infusion meropenem compared with conventional bolus dosing in the management of HAP due to MDR *A. baumannii* **Participants** *N*=30 Adults 19–45 years, middle aged 46–64 years, aged 65–79 years Male: 19, female: 11 Inclusion criteria: HAP due to MDR *A. baumannii* Exclusion criteria: not reported	**Bacteria**: *A. baumanniii* **Resistant to**: carbapenems (meropenem) **Mechanism of resistance**: not reported	**Intervention** Extended intravenous meropenem infusion: 500 mg every 6 h over a 3-h infusion. *N*=15 **Control group** Conventional treatment: intravenous meropenem 1 g. every 8 h over a 1-h infusion. *N*=15 **Length of follow-up**: duration of treatment	**Clinical success/improvement** No significant differences were found between extended-infusion meropenem and conventional bolus dosing in the number of patients with treatment success at days 3, 5 and 7. The rates of relapse also did not significantly differ between the treatment groups **Antibiotic resistance** No patient developed a meropenem-resistant strain of *A. baumannii*, and the MIC_{90} for meropenem against *A. baumannii* remained at 2 µg/mL	**RCT** Acceptable methodological quality (+) Small sample size
Xue 2009 RCT **Setting** Tertiary (one ICU) China June 2007–December 2007	To determine the relation of carbapenem restriction with the incidence of MDR *A. baumannii* in VAP **Participants** *N*=26 Adults 19–45 years, middle aged 46–64 years, aged 65–79 years Male: 15, female: 11 Inclusion criteria: patients receiving mechanical ventilation for more than five days and diagnosed with VAP	**Bacteria**: *A. baumanniii* **Resistant to**: carbapenems **Mechanism of resistance**: ESBL	**Intervention** Carbapenem restriction policy limiting the use of third-generation carbapenems. Only used when severe sepsis and after consultation with a physician from the Department of Infectious Diseases. *N*=12 **Control group** Conventional treatment: no restrictions of carbapenem (doctors were able to prescribe if necessary). *N*=15	**Mortality** The rates of mortality did not differ significantly between the treatment groups (RR 0.78; 95% CI 0.29–2.12). **Antibiotic resistance** More patients in the conventional group developed a carbapenem-resistant strain of *A. baumannii*, although the difference was not statistically significant (RR 0.63; 95% CI 0.38–1.04)	**RCT** Low methodological quality (0) Small sample size

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
	Exclusion criteria: not reported		**Length of follow-up**: duration of treatment		

P. aeruginosa, Pseudomonas aeruginosa; E. coli, Escherichia coli; C. freundii, Citrobacter freundii; M. morgagnii, Morganella morgagnii; A. baumannii, Acinetobacter baumannii; A. anitratus, Acinetobacter anitratus; P. mira, Proteus mira; S.marcescens, Serratia marcescens; B. cepacia, Burkholderia cepacia; MDR, multi-drug resistant; VAP, ventilator-associated pneumonia; ESBL, extended-spectrum beta-lactamase; CMS, colistimethate sodium; RCT, randomized controlled trial; ICU, intensive care unit; UTI, urinary tract infection; HAP, hospital-acquired pneumonia; NSS, nebulized sterile normal saline; CFU, colony-forming unit; SD, standard deviation; RR, risk ratio; CI, confidence interval.

4.4. Systematic Review References

4.4.1.Antimicrobial Stewardship

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4.4.2.Other infection control measures

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4.4.3.Selective decontamination

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4.5. Excluded clinical studies

4.5.1.Case–control study

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4.5.2. Case series/report

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4.5.10. Controlled before–after studies without a minimum of two intervention and control sites

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4.5.11. Interrupted time series studies without at least three data points before and after the intervention

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4.5.12. Participants not relevant

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carbapenem-resistant) *Acinetobacter* infections: a review of the scientific evidence. *J Antimicrob Chemother* 2008;**62**:45–55.

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4.5.13. Antibiotics used not relevant for the review

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Vlieghe E, Phoba MF, Tamfun JJM, Jacobs J. Antibiotic resistance among bacterial pathogens in Central Africa: a review of the published literature between 1955 and 2008. *Int J Antimicrob Agents* 2009;**34**:295–303.

4.5.14. Not multi-drug-resistant infections

Hooton TM, Roberts PL, Stapleton AE. Cefpodoxime vs ciprofloxacin for short-course treatment of acute uncomplicated cystitis: a randomized trial. *JAMA* 2012;**307**:583–589.

Sole Violan J, Fernandez JA, Benitez AB, Cendrero JAC, De Castro FR. Impact of quantitative invasive diagnostic techniques in the management and outcome of mechanically ventilated patients with suspected pneumonia. *Crit Care Med* 2000;**28**:2737–2741.

Appendix 5: CPD material

1. Which of the following are appropriate monotherapy meropenem-sparing agents:

a) Temocillin

b) Cefixime

c) Ceftolozane/tazobactam

d) Fosfomycin

e) Ceftazidime/avibactam

Answer a, c, d, e

2. Which of the following are true:

a) Polymyxins do not require monitoring renal function in the elderly.

b) Fluoroquinolones can be used to treat urinary infection due to multidrug resistant Gram-negative bacteria

c) Oral pivmecillinam should be used alone in the treatment of upper urinary infection

d) Polymyxins should be given in combination with other agents if they are used in treating carbapenem-resistant Enterobacteriaceae.

e) Co-trimoxazole should be used in treatment of infections due to *Stenotrophomonas maltophilia*

Answer b, d, e

3. Which of the following are true:

a) In uncomplicated urinary infection due to a proven ESBL-producing organism, treatment is recommended for 3 days

b) If infection with MDR GNB is suspected, treat asymptomatic bacteriuria

c) Give antibiotic prophylaxis for urinary catheter insertion if previous history of symptomatic urinary infections associated with a catheter change or there is trauma during the catheter insertion

d) Daily antibiotic prophylaxis is preferable to standby antibiotics in recurrent urinary infection

e) Always send a urine specimen for culture if an antibiotic-resistant organism is suspected AND the patient is asymptomatic

Answer c,

4. Which of the following are true;

a) Ceftolozane-tazobactam is active against AmpC producing Enterobacteriaceae

b) Ceftazidime-avibactam is active against AmpC producing#

Enterobacteriaceae

c)KPC-producing *Klebsiella sp*. often produce aminoglycoside

methyltransferases conferring pan-aminoglycoside resistance

d) NDM-producing *E. coli* are usually mecillinam susceptible

e) Proteus sp. are usually resistant to fosfomycin

Answer b

Appendix 6: Consultation stakeholders

Antimicrobial Resistance and Hospital Acquired Infection

Advisory Committee (APRHAI)

British Medical Association

British Society of Antimicrobial Chemotherapy

British Infection Association

C. Diff Support

European Society of Clinical Microbiology and Infectious Diseases

Faculty of Intensive Care Medicine

Foundation Trust Network

Hand Hygiene Alliance

Healthcare Infection Society

Infection Prevention Society

Lee Spark Foundation

MRSA Action UK

NHS Confederation

NHS England

NHS Trust Development Authority

Patient's Association

Public Health England/ Wales/ Scotland/ Northern Ireland

Royal College of Pathologists

Royal College of General Practitioners

Royal College of Nursing

Royal College of Physicians

Royal College of Surgeons

Service User Research Forum Healthcare acquired Infections

UK Clinical Pharmacists Association

Unison

Appendix 7 Response from Stakeholders in consultation

Respondent	Address	Email	Date Rec/d
Conor Doherty	NHS GGC – paed infectious diseases	Conor.Doherty@ggc.scot.nhs.uk	23 May 2016
Ibai Los-Arcos	Infectious Diseases Division, Hospital Universitari Vall d'Hebron Avda. Vall d'Hebron, 119-129 08035 Barcelona. Spain	bai.losarcos@gmail.com	01 June 2016
Prof. Céline PULCINI	Nancy University Hospital, Nancy, France	celine.pulcini@univ-lorraine.fr	01 June 2016
Aaron Nagar	Microbiology Department, Antrim Area Hospital, 45 Bush Rd, Antrim, Northern Ireland, BT41 2RL	Aaron.Nagar@northerntrust.hscni.net	01 June 2016
Dr Paul Chadwick & Dr Alex Peel	Microbiology Department Salford Royal NHS Foundation Trust Stott Lane, Salford. M6 8HD	paul.chadwick@srft.nhs.uk; alex.peel@srft.nhs.uk	15 June 2016
Rebecca Tilley	West Suffolk NHS Foundation Trust, Hardwick Lane, Bury St Edmunds, Suffolk, IP33 2QZ.	rebecca.tilley@wsh.nhs.uk	17 June 2016

Egidia Miftode	Hospital of Infectious Diseases Iasi Str O Botez no 2, code 700274, Iasi Romania	emiftode@yahoo.co.uk	27 June 2016
Neil Woodford	Head, Antimicrobial Resistance and Healthcare Associated Infections Reference Unit (AMRHAI) Public Health England 61 Colindale Avenue London, NW9 5EQ	Neil.Woodford@phe.gov.uk	27 June 2016

British Society for Antimicrobial Chemotherapy
Joint Working Party Paper on Multi resistant Gram-negative Infection: Treatment

Consultation deadline: Friday 17 June 2016

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- Please put each comment in a separate row
- Type directly onto the form. Do not paste other tables or figures as they may get lost
- Only comments received on the attached form will be considered.

How to respond: Please complete this BSAC response form and submit by email to fdrummond@bsac.org.uk no later than **Friday 17 June 2016**. Comments received after the deadline will not be accepted.

Name	Conor Doherty	
Organisation Address & Postcode	NHS GGC – paed infectious diseases	
Email	Conor.doherty@ggc.scot.nhs.uk	

Phone number					
Conflict(s) of Interest		nil			
Document Indicate if you are referring to the **Full** version or the **Appendices**	**Page Number** **Number only** (do not write the word 'page/pg'). Alternatively write **'general'** if your comment relates to the whole document	**Line Number** **Number only** (do not write the word 'line'). See example in cell below	**Comments** **Please insert each comment on a separate row.** **Please do not paste other tables into this table, as your comments could get lost – type directly into this table.**	**Changes:** **Mark as "Exclude" OR "Include" (and reason for change or no change)**	
EXAMPLE: Full	16	45	Our comments are as follows ……	Exclude: Reason	WP Response
			Generally a very useful document. My one concern is that there is no mention of children, infants, neonates. Paeds are increasingly faced particularly with multiresistant G-ve UTI's and the data here is all from all adult studies/perspectives. Unfortunately experience with quite a few of the alternative drugs discussed here is very scant and often appropriate doses/formulations are unknown/unavailable. 1) As a result carabpenem sparing strategies are particularly problematic due to lack of alternatives. I would suggest that the doc either declares itself as 'adult' guidance or discusses this 2) Appropriate empirical treatment and prophylaxis strategies in the face of increasing trimethoprim resistance		Specific mention made that does not cover neonates and mostly does not deal with paediatric dosage or paediatric-specific issues such prophylaxis of UTI

			for paed UTI's is a major issue and not discussed		

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Name	Ibai Los-Arcos	
Organisation Address & Postcode	Infectious Diseases Division, Hospital Universitari Vall d'Hebron Avda. Vall d'Hebron, 119-129 08035 Barcelona. Spain	
Email	ibai.losarcos@gmail.com	

Phone number		0034 93 274 6090			
Conflict(s) of Interest		None			
Document Indicate if you are referring to the **Full** version or the **Appendices**	**Page Number** Alternatively write **'general'** if your comment relates to the whole document	**Line Number** See example in cell below	**Comments** **Please insert each comment on a separate row.** **Please do not paste other tables into this table, as your comments could get lost – type directly into this table.**	**Changes:** **Mark as "Exclude" OR "Include" (and reason for change or no change)**	**WP Response**
Full	61	1651	Mean prostatic fosfomycin levels in the uninflamed peripheral prostatic area after a 3 g dose of fosfomycin trometamol were higher than 4 μg/g in 70% of patients (Gardiner et al. 2014). In addition, fosfomycin-tromethamine monotherapy proved useful for the treatment of 2 cases of MDR Enterobacteriaceae prostatitis (Grayson et al. 2015) and also for the treatment of 53% of patients with difficult-to-treat chronic bacterial prostatitis, including 4/5 (80%) MDR Enterobacteriaceae (Los-Arcos et al. 2015). It could be an alternative agent for the treatment of MDR Enterobacteriaceae prostatitis, in isolates with fosfomycin MICs < 4 μg/ml.	Include	Reference to prostatitis included in fosfomycin section

References:

- Gardiner BJ, Mahony AA, Ellis A G, et al. Is fosfomycin a potential treatment alternative for multidrug-resistant gram-negative prostatitis? Clin Infect Dis 2014;58:e101–5.
- Grayson ML, Macesic N, Trevillyan J, et al. Fosfomycin for treatment of prostatitis: new tricks for old dogs. Clin Infect Dis 2015; 61:1141-3.
- Los-Arcos I, Pigrau C, Rodríguez-Pardo D, et al. Long-term fosfomycin-tromethamine oral therapy for difficult to treat chronic bacterial prostatitis. Antimicrob Agents Chemother 2015; 60: 1854-8.

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- Type directly onto the form. Do not paste other tables or figures as they may get lost
- Only comments received on the attached form will be considered.

How to respond: Please complete this BSAC response form and submit by email to fdrummond@bsac.org.uk no later than **Friday 17 June 2016**. Comments received after the deadline will not be accepted.

Name	Prof. Céline PULCINI	
Organisation Address & Postcode	Nancy University Hospital, Nancy, France	
Email	celine.pulcini@univ-lorraine.fr	
Phone number		
Conflict(s) of Interest	None	

Document Indicate if you are referring to the **Full** version or the **Appendices**	**Page Number** Alternatively write **'general'** if your comment relates to the whole document	**Line Number** See example in cell below	**Comments** **Please insert each comment on a separate row.** **Please do not paste other tables into this table, as your comments could get lost – type directly into this table.**	**Changes:** **Mark as "Exclude" OR "Include" (and reason for change or no change)**	
EXAMPLE: Full	16	45	Our comments are as follows ……	Exclude: Reason	WP Response
Full	general		Congratulations on your hard work! I miss a summary of the recommended dosing and durations of treatment for each antibiotic and I feel that a section on optimised PK/PD (prolonged infusions…) would be a plus		Dosing recommendations uness specifically otherwise referenced are as per product medicines license and outside scope of WP Report. Some information on prolonged infusion of meropenem now included but full section rather than illustration of benefit outside scope of WP

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Name	Aaron Nagar	
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Phone number	02894424113	
Conflict(s) of Interest	Speaker fee from Astellas	

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EXAMPLE: Full	16	45	Our comments are as follows ……	Exclude: Reason	WP Response
Full	40	1086	Change to "Ceftazidime –avibactam may be used as an alternative to carbapenems in exceptional circumstances i.e. infection with KPC producer"	Include: Though evidence is not there feel that Ceftazidime-avibactam should be reserved for infections for which there are limited options .i.e. KPC producers. Given targets to reduce carbapenem use, I fear ceftazidime-avibactam may be overused driving resistance to it.	Review is required to be evidence-based by NICE
Full	64	1743	Suggest changing the order of the oral agents i.e. nitrofurantoin, pivmecillinam and fosfomycin	Include: Feel this order is better as people tend to use the first agent in a guideline more. Feel that fosfomycin should be last as we may have to use the IV form more when CPE becomes more prevalent. It will not be useful if we drive resistance by PO fosfomycin overuse.	Order specified in new algorithm
Full	65	1754	Feel that the order of PO agents in the text should be changed to nitrofurantoin, pivmecillinam and fosfomycin	Include: Feel this order is better as people tend to use the first agent in a guideline more i.e. feel	Order specified in algorithm

				that it indicates preference. Feel that fosfomycin should be last as we may have to use the IV form more when CPE becomes more prevalent. It will not be useful if we drive resistance by PO fosfomycin overuse.	
Full	65	1756	Feel that we should remove 7 days treatment for uncomplicated UTI due to an ESBL producer	Exclude: Feel that clinical staff over treat older patients with asymptomatic bacteriuria and are always looking for excuses to extend duration. I feel we should stick with shorter durations for symptomatic cure.	Comment is not evidence-based. WP specifically considered that bacteriologically optimum treatement required when MDR GNB being treated but not generally
Full	81	2179	Feel that we should discourage dipstick use in patients over 65 years of age as per SIGN guidance	Exclude: Find it very difficult to convince clinicians not to use urine dipstick to diagnose and treat asymptomatic bacteriuria as UTI.	Agree with specific point about asymptomatic bacteriuria and this has been added. Detailed technology review consideration of dipsticks in paper extended and changed

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How to respond: Please complete this BSAC response form and submit by email to fdrummond@bsac.org.uk no later than **Friday 17 June 2016**. Comments received after the deadline will not be accepted.

Name	Dr Paul Chadwick, Clinical lead/consultant microbiologist Dr Alex Peel, Antimicrobial stewardship lead/consultant microbiologist	
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Conflict(s) of Interest		

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Full	general		This guideline is welcomed as a resource to support treatment of MDR Gram negative infections and is supported by an extensive literature review. However, the recommendations in their current form appear as a fairly disjointed and inconsistent collection of statements. For example, the first recommendation starts with the role of temocillin vs Enterobacteria and Burkholderia and the second recommendation is for ampicillin-sulbactam vs Acinetobacter. This is not a logical or helpful sequence for presentation. Some of the recommendations appear as a surprise as they do not relate back to the preceding evidence or discussion. Care should be taken to ensure that this link is made and a justification provided for all recommendations Perhaps the functionality of the guideline could be improved with a more structured approach to the management of MDR Gram negatives? For example the role of each of the different classes of agents (recommended Y/N + comments) could be systematically presented as a table for each of the common resistance mechanisms, if necessary separated into different tables for the		Very useful set of comments. 1. Antibiotics considered have been re-ordered to reflect important issues. 2. All recommendation checked for relationship to text and evidence 3. Too many mechanisms to consider all but additional table on mechanisms and activity added.

			different organism groups (e.g. Enterobacteria, non-fermentors).		
Full	28	783	The conclusion that temocillin may be used as a carbapenem-sparing agent against Enterobacteria is (a reasonable) opinion of the authors but does not follow from the evidence presented. (The same opinion might also have be given for other classes of agent such as polymixins). Consideration should be given to simplifying and rephrasing the recommendation to 'temocillin can be used to treat infections due to Enterobacteria, including ESBL and AmpC producers'		Considered on a case by case basis
Full	30	830	The recommendation that 'Amoxicillin-clavulanate should not be used to treat infection with known ESBL-producing organism unless sensitivity known ' is generally not very helpful for a typical diagnostic laboratory where apparent co-amoxiclav susceptibility will be known either before or at the same time as ESBL production is confirmed. Alternatively, if the authors are suggesting that a patient with a history of ESBL positive UTI/infection should not be given co-amoxiclav until sensitivity for the current episode is confirmed, the recommendation should be clearly reworded		Detailed consideration given of this recommendation but given 6+% recurrence rate with ESBL infection previous susceptibility is an important factor in making this choice. Substantual cavaeats against use of coamoxiclav and piperacillin/tazobactam use in UK added both because of in vitro resistance and prevalence pf OXA-1 in UK isolates
Full	32	883	The following recommendation is not supported by any evidence linking clinical outcomes to sepsis severity criteria: 'Piperacillin-tazobactam can be considered for use in mild-moderate infections (i.e. not severe sepsis) due to ESBL-producing Enterobacteriaceae if supported by susceptibility results.' The evidence should be provided, the opinion justified, or the recommendation removed.		Recommendation changed to omit reference to severity of infection
Full	32	888	The following recommendation is not supported by any evidence. …'However combination with an aminoglycoside is advisable for severe infections.' The evidence		Agree. Removed

			should be provided, the opinion justified, or the recommendation removed.		
Full	36	986	It is unclear why there needs to be a separate recommendation for ertapenem: 'Ertapenem is effective in treatment of infections with multi-resistant Enterobacteriaceae apart from carbapenemase producers' when this has apready been covered by the previous recommendation: ' Carbapenems should be used to treat serious ESBL-producing Gram-negative infections subject to antibiotic stewardship to minimize the risk of developing resistance'. Is there a reason why the general carbapenem recommendation is not extended to include AmpC resistance? For internal consistency within the document, we suggest merging these two recommendations as follow: 'carbapenems can be used to treat infections due to ESBL or AmpC producing Enterobacteria'.		Ertapenem has different properties and is now recommended for OPAT. AmpC issue now considered
Full	37	1010	The format of the following recommendation is internally inconsistent within the document: 'Although it retains good efficacy against infections with *Pseudomonas aeruginosa*, ceftazidime is not recommended for the treatment of other serious infections due to ESBL / AmpC producing Enterobacteriaceae, even if in vitro tests suggest the isolate is susceptible.' We suggest 1) separating the recommendations for treating Pseudomonas and Enterobacterial infections, 2) rephrasing the recommendation for Enterobacteria as follows: 'ceftazidime should NOT be used to treat infections due to ESBL or AmpC producing Enterobacteria'		rephrased
Full	39	1074	Information relating to aztreonam-avibactam, while interesting, does not belong under a heading of ceftazidime-avibactam and is not		Separate aztreonam section added whoich houses the experimental

			directly relevant to the guideline – suggest remove		combination aztreoname-avibactam
Full	40	1086	The format of the following recommendation is internally inconsistent within the document: 'With the exception of infections with metallo-β-lactamase strains, ceftazidime-avibactam, when available, should be used as alternative treatment to carbapenems'. We suggest rephrase this recommendation as follows: 'ceftazidime-avibactam can be used to treat infections due to Enterobacteria, including ESBL and AmpC producers'		Rewritten
Full	42	1140	The format of the following recommendation is internally inconsistent within the document (and implies that it should be used in preference to carbapenems): 'Ceftolozane-tazobactam should be used as alternative treatment to carbapenems in treating ESBL-producing Gram negative pathogens (but not carbapenemase producers). We suggest rephrase this recommendation as follows: 'ceftolozane-tazobactam can be used to treat infections due to Enterobacteria, including ESBL and AmpC producers'		Rewritten
Full	45	1231	There is potential overlap/duplication regarding combination therapy with this recommendation and the recommendation on page 56, line1518. Consider either removing 'and preferably used in combination with other agents' and adding a cross reference to the later section		Cross-references inserted where useful
Full	45	1234	The recommendation with regard to renal function is internally inconsistent within the document as side effects are not systematically considered for other agents. Many important unwanted effects occur for many different antimicrobials and relevant monitoring should be considered as a matter of course by the prescribing clinician (and this might include monitoring colistin levels also,		To contaienm a;lready voluminous length Unwanted effects are highlighted where may be specifically over-looked.

			which is not mentioned as a recommendation).		
Full	46	1266	The format of the following recommendation is internally inconsistent within the document: 'Fluoroquinolones can be used to treat urinary infection due to multidrug resistant Gram-negative bacteria based on susceptibility results.' We suggest rephrase this recommendation as follows: 'quinolones can be used to treat complicated urinary tract infections due to Gram negative bacteria'		Standardised
Full	51	1390	The format of the following recommendation is internally inconsistent within the document: 'Fosfomycin should be used in treatment of urinary infection due to multiresistant Gram-negative bacteria (oral administration only suitable for lower urinary infection)' We suggest rephrase as follows: 'Fosfomycin can be used to treat urinary tract infections due to Gram-negative bacteria (oral administration only suitable for lower urinary infection)'		Standardised
Full	52	1410	To improve internal consistency within the document, we suggest adding the following additional recommendation (which follows from the preceding evidence): 'aztreonam should NOT be used to treat infections due to ESBL or AmpC producing Enterobacteria'		Agreed
Full	65	1758	There is a recommendation to use 7 days therapy for ESBL simple UTIs to improve bacteriological clearance. There is no mention of clinical outcomes evidence. Bacteriological clearance does not necessarily correlate well with clinical outcomes (e.g. high prevalence of asymptomatic bacteriuria in certain patient populations). This recommendation could lead to a large increase in ab use if implemented widely and		Debated at length within WP. Considered that best possible bacteriological clearance should be obtained with proven MDR GNB infection but caveat inserted about clinical relevance of bacteriological cure.

			it would need strong clinical evidence before doing so.		
Full	66	1795	This recommendation: 'admission for intravenous aminoglycoside therapy' is potentially confusing as it appears to exclude an inpatient carbapenem option (presumably temocillin or other agents recommended above for Enterobacteria could also be considered). We suggest rephrase as 'admission for intravenous therapy with an aminoglycoside or carbapenem (? Or temocillin etc)		Whole section fo recommendations recast. Point accepted.
Full	General	General	Although the evidence base is weak in many areas, and the authors are to be commended for covering many topic areas, we feel the document does not read like it is focused on an infection specialist dealing with 'real world' problems e.g. a patient with KPC bacteraemia with MICs of x,y,z and renal failure and obesity etc – we note that the US has produced flowcharts previously (e.g. Medscape http://www.medscape.com/viewarticle/780065_9) see screenshot on following page, and more recent publications - clearly these may be based on minimal evidence but they do provide a start. We wonder whether consideration could be given by the WP to producing similar tools.		" simple flow-charts inserted but subject is too diverse to deal with all possible clinical situations

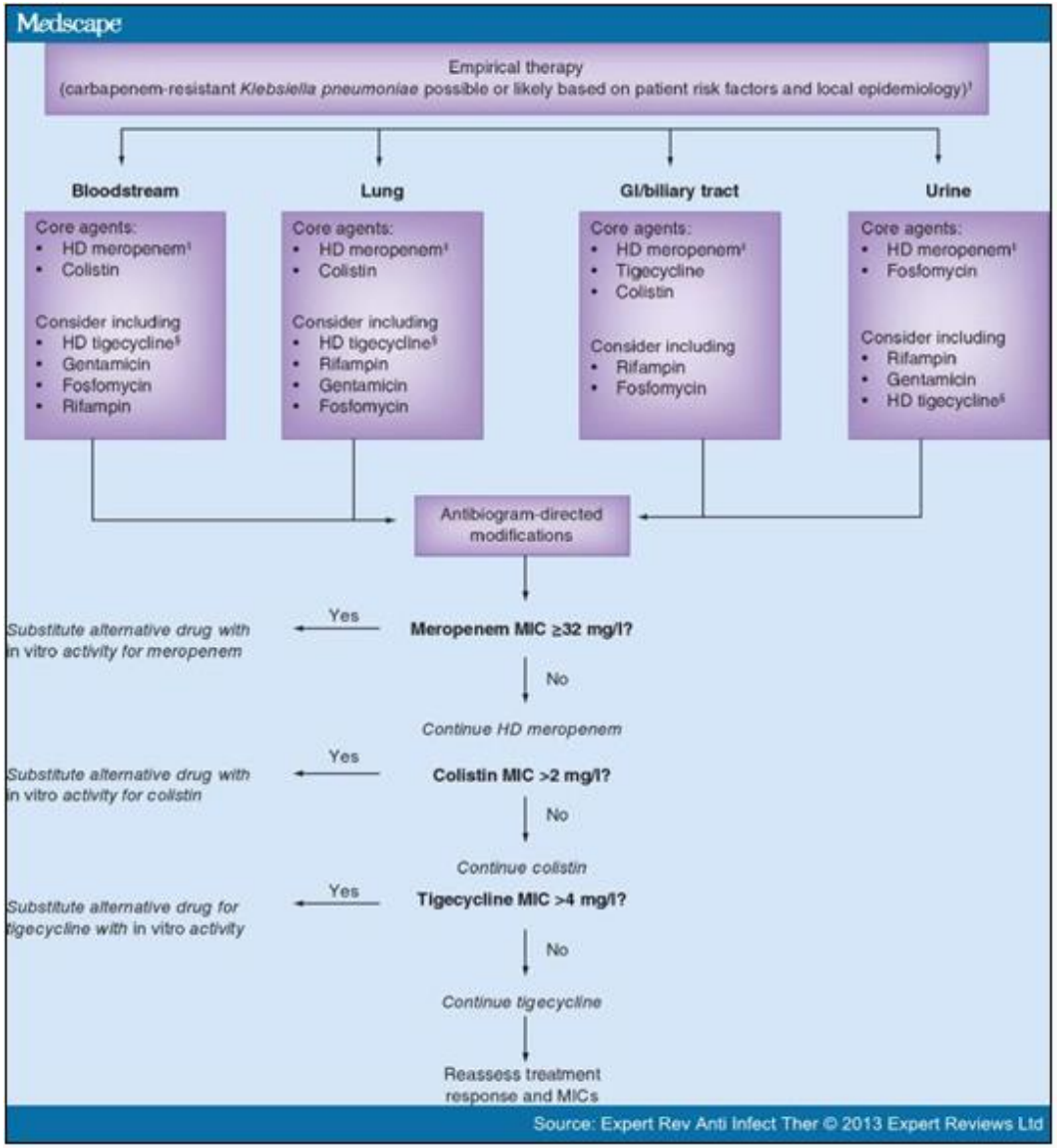

Figure 2.

Potential antibiotic combination therapy algorithm for the treatment of carbapenem-resistant *Klebsiella pneumoniae* infections stratified to site of infection and antibiogram results. †Algorithm would be appropriate for institution where >50% of isolates exhibit carbapenem MICs in the treatable range with HD therapy (MIC <32 mg/ml). Specific drugs used for empirical therapy should be tailored the epidemiology of endemic carbapenem-resistant *Klebsiella pneumoniae* strains.‡HD meropenem (6 g daily, administered as prolonged infusion).§HD tigecycline (200 mg loading dose, 100 mg once a day), see text regarding the limitations and evidence supporting the use of HD regimens.HD: High-dose.

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Name	Rebecca Tilley	
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Conflict(s) of Interest	None	

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EXAMPLE: Full	16	45	Our comments are as follows ……	Exclude: Reason	WP Response
Full	15	423	Typo – "uin" instead of "in"	Exclude: correct the spelling	All typos dealt with
Full	38	1054	Typo – "Gram-egative" instead of "Gram-negative"	Exclude: correct the spelling	All typos dealt with
Full	52	1415	Typo – "mecillianam" instead of "mecillinam"	Exclude: correct the spelling	All typos dealt with
Full	74-75	2004-2009	All bacteraemias or just MRGN bacteraemias? This would require a standardised format to enable direct comparison but is also a very complex, multifactorial issue and would also need to capture sufficient clinical detail e.g. not all mortality is a result of inappropriate antibiotic prescribing; blood cultures often signal positive after the patient has died plus were there risk factors for MRGN identified during primary assessment? This also sounds a very labour intensive requirement. Please be aware that many microbiology consultants are already having to collate a lot of information as a mandatory requirement for bodies such as PHE without any additional resources being identified and would struggle to add more to the pile. Not all departments have junior doctors to assist with this sort of responsibility.	Exclude: needs modifying. Please specify whether all bacteraemias or not and give appropriate consideration to format and additional resources required, particularly if this were to become a mandatory requirement, to support business cases within local Trusts.	Accept point on consultant time and specifically added but priority of required action and information on Gram-negative bacteraemias is high. Extensive bacteraemia information added and advice taken from BIA.

Full	82	2194	Would recommend that 1) the term “standby antibiotics” is explained and 2) that advice is given on how a clinician, bearing in mind this is often a GP, would decide which antibiotic would be appropriate as a “standby” option.	Exclude: Needs modification.	Clarified
Full	90	2246	There is a superscript β in the flowchart, but it does not appear to refer to anything	Exclude: Needs reviewing	Dealt with
Full	90	2252	There is a comment marked ¥, but this symbol does not appear in the flowchart.	Exclude: needs reviewing	Dealt with
Full	General		MRGNs are an increasing problem for us but we are not yet seeing many MRGN bacteraemias and CPEs remain very rare locally. The management of sepsis necessarily requires empirical broad-spectrum antibiotic treatment before we have positive microbiology but we are not yet at the stage where our local guidance advises empirical cover for MRGNs unless there are risk factors for this. We are concerned that the recent CQUIN – re: reduction in antibiotic consumption which is particularly targeting piperacillin-tazobactam and carbapenems seems to be at odds with the empirical management of sepsis and if our Trust has any hope of achieving this target (which incidentally uses historic baseline data from a time when MRGNs were far less prevalent) then we would need to be moving empirical therapy back to cephalosorins and quinolones for example. We are reluctant to do this from a C. difficile perspective and from driving resistance mechanisms yet further. We appreciate that this document is not directly related to the CQUIN and that we are venting our frustration but it would be helpful if BSAC could issue a position statement or guidance on this CQUIN and outline the best approach for microbiologists to a) do the right thing in terms of empirical therapy for the septic patient, particularly if there is a MRGN risk plus b) reduce the risk of promoting antibiotic resistance plus c) meet contractual obligations. I know we are not the only Trust		We are also concerned about the potneital conflict between antibiotic-use reduction targets and potential mortality in bacteraemia which has similar 30 day mortality to C.difficile. Document extensively revised and your general points incorporated. Thank you

			that is exasperated by the specifics within this DH requirement which seems to totally disregard all the improvements made in recent years with regard to C. difficile and antibiotic stewardship.		
Full	General		The document discusses using antibiotics such as temocillin, tigecycline, colisitin and fosfomycin. EUCAST does not provide guidance on interpretation of temocillin susceptibility either by disk or MIC. Tigecycline needs to be tested via MIC for anything other than E coli. Fosfomycin & colistin need to be tested by MIC. These requirements reduce the turnaround times for results. In addition, the turnaround times for CPE resistance mechanisms/additional sensitivities do not help support optimum patient management. Could PHE Colindale publish its testing methods/MIC interpretations to enable local testing rather than sending isolates to them? Is there a way to expedite EUCAST guidance on temocillin interpretations? Can BSAC offer recommendations to support local business cases for introducing technology that enables faster identification of e.g. CPEs in house as opposed to relying on reference laboratories?		In practice we now consider that molecular methodology is needed for colistin susceptibility testing and MICs for meropenem with MDR GNB and this has been added. To track the fast changing situation we have now recommended that i) mandatory reporting of carbapenem resistant isolates is introduced ii) isolates are dealt with expeditiously for patient benefit and iii) isolates referred where testing is beyond the scope of local laboratories.

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Conflict(s) of Interest	none	

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EXAMPLE: Full	16	45	Our comments are as follows ……	Exclude: Reason	WP response
Full	56	1515	Klebsiella pneumoniae carbapenemase-producing		Dealt with
full	47	1292	compared		Dealt with

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Name		Neil Woodford			
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Conflict(s) of Interest					
Document Indicate if you are referring to the **Full** version or the **Appendices**	**Page Number** **Number only** (do not write the word 'page/pg'). Alternatively write **'general'** if your comment relates to the whole document	**Line Number** **Number only** (do not write the word 'line'). See example in cell below	**Comments** **Please insert each comment on a separate row.** **Please do not paste other tables into this table, as your comments could get lost – type directly into this table.**	**Changes:** **Mark as "Exclude" OR "Include" (and reason for change or no change)**	**WP Response**
Full	Many	Many	Group the urinary tract infection summaries and cephalosporin/antibiotic summaries	Include	Sections extensively re-ordered
Full	Many	Many	The referencing seems to be sporadic, with some areas very well referenced and others less so or not at all. A consistent approach throughout would be beneficial e.g. more references for UK statements in Pages 624-634	Include	Re-referenced and numerous references added
Full	Many	Many	Quite a lot of sections do not have an added line break following a new paragraph	Include	Line breaks removed for JAC
Full	Many	Many	After evidence and recommendations sometimes there are bullet points and other times not – consistency would be good	Include	Consistent approach adopted
Full	5	163	Infection also happens through bacteria gaining access to organs or bloodstream from internal sources e.g. gut translocation	Include	Evidence for translocation in absence of local infection is poor

Full	11	322	Extra space between ‘tazobactam’ and ‘should’	Exclude	Typos dealt with
Full	13	370	Full stop required after ‘resistance’	Include	Typos dealt with
Full	13	381	Extra space between ‘of’ and ‘new’	Exclude	Typos dealt with
Full	13	388	Extra comma between ‘the’ and ‘community’	Exclude	Typos dealt with
Full	14	404	Full stop required after ‘incontinence’	Include	Typos dealt with
Full	15	423	Extra u in ‘uin’	Exclude	Typos dealt with
Full	17	471	Extra space between ‘treatment’ and ‘,’	Exclude	Typos dealt with
Full	17	483	Full stop required after ‘(Table 2)’	Include	Typos dealt with
Full	2	131	No Appendix 5 listed	Include	Appendices renumbered and referred to in text
Full	18	505	Extra comma required between ‘required’ and ‘notably’	Include	Typos dealt with
Full	18	505	Extra comma between ‘.’ and ‘There’	Exclude	Typos dealt with
Full	23	643	Extra space required between ‘2009,’ and ‘and’	Include	Typos dealt with
Full	25	685	Et al should be italicised	Include	Typos dealt with
Full	25	694	Extra space between ‘5%’ and ‘)’	Exclude	Typos dealt with
Full	26	702	Extra space between ‘imported’ and ‘to’	Exclude	Typos dealt with
Full	26	733	Extra space required between ‘compare,’ and ‘(’	Include	Typos dealt with
Full	30	817	Extra space between ‘the’ and ‘study’	Exclude	Typos dealt with
Full	30	819	Extra space between ‘MICs’ and ‘to’	Exclude	Typos dealt with
Full	32	879	Extra space between ‘bactam’ and ‘is’	Exclude	Typos dealt with
Full	33	917	Extra full stop after ‘ceftazidime’ and‘.’	Exclude	Typos dealt with
Full	35	960	Extra space between ‘isolates’ and ‘of’	Exclude	Typos dealt with
Full	35	967	Extra comma between ‘result’ and ‘(Hyle)’	Exclude	Typos dealt with
Full	35	973	Extra space between ‘did’ and ‘not’	Exclude	Typos dealt with
Full	37	1024	Extra space between ‘responded’ and ‘.’	Exclude	Typos dealt with
Full	38	1044	Extra space required between ‘Eve’ and ‘in’	Include	Typos dealt with
Full	39	1066	Extra space between ‘lactamases’ and ‘(NDM’	Exclude	Typos dealt with
Full	39	1078	Extra space between ‘trials’ and ‘,’	Exclude	Typos dealt with
Full	40	1097	Extra space between ‘aeruginosa’ and ‘with’	Exclude	Typos dealt with
Full	42	1140	Extra space between ‘bactam’ and ‘should’	Exclude	Typos dealt with
Full	43	1184	Extra space between ‘period’ and ‘(Huttner’	Exclude	Typos dealt with
Full	44	1211	Extra space required between ‘toxicity’ and ‘(Kelesidis’	Include	Typos dealt with
Full	46	1246	Extra space between ‘quinolones’ and ‘,’	Exclude	Typos dealt with
Full	46	1255	Extra space between ‘used’ and ‘to’	Exclude	Typos dealt with
Full	47	1276	Extra space between ‘most’ and ‘Enterobacteriaceae’	Exclude	Typos dealt with

Full	48	1309	Extra space between 'Tumbarello' and '*et al*'	Exclude	Typos dealt with
Full	49	1345	Extra space between 'activity' and ':'	Exclude	Typos dealt with
Full	50	1370	Extra space between 'gentamicin' and '('	Exclude	Typos dealt with
Full	56	1518	Should 'except rifampicin' be included in the recommendation for combination therapy with colistin	Include	Considered but dealt with in text
Full	56-57	1539-1543	Is this truly accurate of UK practice. Internal work at St Thomas' Hospital several years ago highlighted much higher resistance rates than this.	Include	Agree. Modified with additional references
Full	60	1624	Extra space between 'GI' and 'effects'	Exclude	Typos dealt with
Full	60	1630	Extra space between 'factors' and 'that'	Exclude	Typos dealt with
Full	56-63	N/A	Should there be a section on the use of sterilising agents or the use of NSAIDs in uncomplicated UTIs	Include	Probably not as emphasis is primarily on serious infection
Full	64	1738	Extra space between 'cure' and 'Brayfield'	Exclude	Typos dealt with
Full	67	1824	Extra space between 'or' and 'carbapenem'	Exclude	Typos dealt with
Full	67	1826	Extra space between 'situations' and ','	Exclude	Typos dealt with
Full	68	1852	Extra space between 'appropriate' and ','	Exclude	Typos dealt with
Full	68	1857	Extra space between 'institutions' and ','	Exclude	Typos dealt with
Full	69	1862	Extra space between 'and' and 'accounts'	Exclude	Typos dealt with
Full	70	1890	Extra space between 'One' and 'controlled'	Exclude	Typos dealt with
Full	70	1892	Extra space between 'most' and 'studies'	Exclude	Typos dealt with
Full	70	1898	Extra space between 'trials' and ','	Exclude	Typos dealt with
Full	71	1917	Extra space between 'few' and 'studies'	Exclude	Typos dealt with
Full	75	2011	Extra space between 'of' and 'new'	Exclude	Typos dealt with
Full	76	2053	Extra space between '%' and 'absolute'	Exclude	Typos dealt with
Full	78	2088	Extra space required between ')' and 'in'	Include	Typos dealt with
Full	78	2107	Extra space required between 'bacteriuria' , which also needs an I removed, and 'in'	Include/Exclude/Respell	Typos dealt with
Full	78	2110	Extra space between 'of' and 'colonisation'	Exclude	Typos dealt with
Full	80	2135	Extra space between 'resistance' and '.'	Exclude	Typos dealt with
Full	80	2147	Extra space between 'resistance' and '.'	Exclude	Typos dealt with
Full	80	2148	Extra space between 'on' and 'consensus'	Exclude	Typos dealt with
Full	80	2147	Full stop needed after 'i'	Include	Typos dealt with
Full	81	2167	Extra space between 'infection' and 'but'	Exclude	Typos dealt with
Full	81-83	N/A	Should there again be a section on the use of sterilising agents or the use of NSAIDs in uncomplicated UTIs	Include	See previous response
Full	84	2217	Extra space required between 'studies' and '(SIGN'	Include	Typos dealt with

Full	85	2224	Extra space required between ‘grading’ and ‘(SIGN’, which is also superscripted unnecessarily	Include	Typos dealt with
Full	85	2225	Table sometimes has full stop and at other times does not	Include	Hopefully dealt with