

Draft for consultation

Antimicrobial stewardship

**Antimicrobial stewardship: systems and
processes for effective antimicrobial
medicine use**

Medicines practice guideline

Methods, evidence and recommendations

February 2015

Draft for consultation

*National Institute for Health and Care
Excellence*

Disclaimer

This guideline represents the views of NICE and was arrived at after careful consideration of the evidence available. Those working in the NHS, local authorities, the wider public, voluntary and community sectors and the private sector should take it into account when carrying out their professional, managerial or voluntary duties.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Copyright

National Institute for Health and Care Excellence 2015

Contents

The Guideline Development Group and NICE project team	6
Acknowledgements.....	8
1 Introduction	9
1.1 Background and policy context.....	9
1.2 Legal framework.....	11
1.2.1 Regulatory requirements.....	11
1.3 Definitions used in the guideline	11
1.4 Person-centred care.....	12
1.5 Strength of recommendations.....	13
1.5.1 Recommendations using ‘should’ (or ‘should not’) – ‘strong’ recommendations	13
1.5.2 Recommendations using ‘should consider’	13
2 Development of a NICE guideline.....	14
2.1 What is a NICE medicines practice guideline?	14
2.2 Remit.....	15
2.3 Who developed the guideline	15
2.4 Purpose and audience.....	15
2.5 What this guideline covers.....	15
2.6 What this guideline does not cover	16
2.7 Related NICE guidance	16
2.7.1 Published	16
2.7.2 Under development.....	17
3 Methods	18
3.1 Developing review questions and outcomes.....	18
3.1.1 Review questions.....	18
3.1.2 Writing the review protocols	19
3.2 Searching for evidence.....	20
3.2.1 Clinical and health economic literature searching.....	20
3.3 Reviewing the evidence.....	20
3.3.1 Inclusion and exclusion criteria	20
3.3.2 Methods of combining clinical studies	20
3.3.3 Types of studies.....	21
3.3.4 Call for evidence	21
3.3.5 Appraising the quality of evidence by outcomes.....	21
3.3.6 Evidence statements (summarising and presenting results for effectiveness).....	22
3.4 Evidence of cost effectiveness	23
3.5 Developing recommendations	23
3.6 Research recommendations.....	24

3.7	Validation review	24
3.7.1	Validation process.....	24
3.7.2	Updating the guideline	24
3.7.3	Disclaimer	24
3.7.4	Funding.....	24
4	Guideline summary	25
4.1	Implementation section.....	25
4.2	Full list of recommendations	25
4.2.1	Research recommendations	31
5	Reducing antimicrobial resistance	33
5.1	Introduction	33
5.2	Review question	34
5.3	Evidence review	34
5.3.1	Clinical evidence	34
5.3.2	Health economic evidence	41
5.4	Evidence statements	41
5.4.1	Clinical outcomes.....	41
5.4.2	Economic evidence	42
5.5	Evidence to recommendations	42
5.6	Recommendations and research recommendations.....	51
5.6.1	Recommendations	51
5.6.2	Research recommendations	51
6	Decision-making.....	55
6.1	Introduction	55
6.2	Review question	55
6.3	Evidence review	55
6.3.1	Clinical evidence	55
6.3.2	Health economic evidence	59
6.4	Evidence statements	64
6.4.1	Clinical evidence	64
6.4.2	Economic evidence	65
6.5	Evidence to recommendations	65
6.6	Recommendations and research recommendations.....	70
6.6.1	Recommendations	70
6.6.2	Research recommendations	70
7	Barriers to decision-making	72
7.1	Introduction	72
7.2	Review question.....	72

7.3	Evidence review	72
7.3.1	Clinical evidence	72
7.3.2	Analysis of the included studies	77
7.4	Health economic evidence	83
7.5	Evidence statements	83
7.5.1	Clinical evidence	83
7.6	Evidence to recommendations	83
7.7	Recommendations and research recommendations	90
8	Timely adoption and diffusion of a new antimicrobial.....	91
8.1	Introduction	91
8.2	Review question	91
8.3	Evidence review	92
8.3.1	Clinical evidence	92
8.3.2	Additional evidence	94
8.3.3	Health economic evidence	104
8.4	Evidence statements	104
8.4.1	Clinical evidence	104
8.4.2	Call for evidence	104
8.4.3	Economic evidence	105
8.5	Evidence to recommendations	105
8.6	Recommendations and research recommendations	113
9	References.....	114
10	Glossary.....	119

The Guideline Development Group and NICE project team

Guideline Development Group

Name	Role
Chris Cefai	Consultant in Clinical Microbiology and Infection Control, Betsi Cadwaladr University Health Board, North Wales
Esmita Charani (until 27 November 2014)	Academic Research Pharmacist, National Centre for Infection Prevention and Management, Imperial College London and Honorary Clinical Pharmacist, Imperial College Healthcare NHS Trust
Lynne Craven	Lay member
Martin Duerden	Sessional/Locum GP, North Wales, Clinical Senior Lecturer, Centre for Health Economics and Medicines Evaluation, Bangor University
Heather Edmonds	Lead Medicines Optimisation and Antimicrobial Pharmacist, Leeds North Clinical Commissioning Group
Alastair Hay (Chair)	Professor of Primary Care and NIHR Research Professor, Centre for Academic Primary Care, School of Social and Community Medicine, University of Bristol; and GP, Concord Medical Centre, Bristol
Philip Howard	Consultant Antimicrobial Pharmacist, Leeds Teaching Hospitals NHS Trust
Sanjay Kalra	Consultant in Trauma and Orthopaedics and Clinical Lead for Infection Control, Royal Liverpool University Hospitals NHS Trust
Tessa Lewis (Vice-Chair)	GP and Medical Advisor to All Wales Therapeutics and Toxicology Centre
Kym Lowder	Head of Medicines Management, Integrated Care 24 Limited, Kent
Clodna McNulty	Head of Primary Care Unit, Public Health England
John Morris	Lay member
Sanjay Patel	Consultant in Paediatric Infectious Diseases and Immunology, University Hospital Southampton NHS Foundation Trust
Wendy Thompson	Associate Dentist, Sedbergh Dental Practice, Clinical Supervisor, Blackpool Teaching Hospitals NHS Foundation Trust, Lecturer in Antimicrobial Prescribing, Health Education NE
Susan Walsh	Lay Member

NICE project team

Name	Role
Leighton Coombs	Data Analyst, Health Technology Intelligence, NICE
Johanna Hulme	Project Lead and Associate Director, Medicines and Prescribing Centre, NICE
Debra Hunter	Assistant Project Manager, Medicines and Prescribing Centre, NICE (from 29 September 2014)
Dominick Moran	Data Analyst, Costing and Commissioning Implementation, NICE
Greg Moran	Senior Adviser, Medicines and Prescribing Centre, NICE
Roberta Richey	Senior Adviser, Medicines and Prescribing Centre, NICE (from 1 August 2014)
Rebekah Robinson	Assistant Project Manager, Medicines and Prescribing Centre, NICE (until 26

Name	Role
	September 2014)
Emma Aaron	Administrator, Medicines and Prescribing Centre, NICE

1

Acknowledgements

2

The Guideline Development Group would like to thank all the respondents who contributed to the call for evidence.

3

4

1 Introduction

1.1 Background and policy context

Since 1998, when the first World Health Assembly [antimicrobial resistance resolution](#) was agreed, there has been increasing national and international awareness of the need to consider the appropriate use of antimicrobials. The balance between using antimicrobials appropriately and reducing use where they are not indicated is difficult. There are concerns about possible harm to people if treatment is not given. But there is agreement about the need to raise awareness of the increase in antimicrobial resistance associated with prescribing antimicrobials. Antimicrobial stewardship requires a system-wide approach with individuals and organisations promoting and monitoring the judicious use of antimicrobials; by doing this it is hoped that their future effectiveness can be preserved.

Antimicrobial resistance – background

In 2014 Public Health England (PHE) published the [English surveillance programme antimicrobial utilisation and resistance \(ESPAUR\) report](#). The report highlights that ‘antibiotics are unlike other drugs used in medicine, as the more we use them the less effective they become. This is because overuse gives resistant bacteria a greater chance to survive and spread.’ The report states that ‘antibiotic prescribing has increased in England year on year’ and that although there is variability across England for antimicrobial resistance and antimicrobial prescribing, ‘frequently areas with high prescribing also have high resistance’.

The [Executive Board of the World Health Organization](#) considers antimicrobial resistance to be the ‘loss of effectiveness of any anti-infective medicine, including antiviral, antifungal, antibacterial and antiparasitic medicines’ and states that ‘resistant infection may kill, can spread to others, and imposes huge costs to individuals and society.’

The [annual report of the Chief Medical Officer, volume two, 2011: Infections and the rise of antimicrobial resistance](#) states that ‘resistance of microorganisms to our drugs is increasing’ and ‘the supply of new replacement antimicrobial agents has slowed dramatically’ meaning that in future we may have ‘far fewer options in the treatment of infectious disease and infections’. The report calls for ‘better antimicrobial stewardship to preserve the effectiveness of antibiotics’ and describes this as a major mechanism for addressing antimicrobial resistance.

The CMO report states that antimicrobial stewardship ‘embodies an organisational or healthcare-system-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness’. The report also describes 3 major goals that have been identified for antimicrobial stewardship, to:

- optimise therapy for individual patients
- prevent overuse, misuse and abuse, and
- minimise development of resistance at patient and community levels.

Policy context

The [annual report of the Chief Medical Officer, volume two, 2011: Infections and the rise of antimicrobial resistance](#) sets out the challenges and opportunities in the prevention, diagnosis and management of infectious diseases. It sets out recommendations relating to

1 the emergence of microorganisms (bacteria, viruses, fungi and parasites) that are resistant to
2 antimicrobials.

3 In 2013, the Department of Health published the [UK five year antimicrobial resistance](#)
4 [strategy 2013 to 2018](#), which aims to slow the development and spread of antimicrobial
5 resistance. The strategy states that antimicrobial resistance cannot be eradicated, but by
6 using a multidisciplinary approach, the risk of antimicrobial resistance can be limited and its
7 impact on health now and in the future can be reduced. The report describes 3 strategic
8 aims, to:

- 9 • improve the knowledge and understanding of antimicrobial resistance
- 10 • conserve and steward the effectiveness of existing treatments
- 11 • stimulate the development of new antibiotics, diagnostics and novel therapies.

12 An [antimicrobial resistance strategy impact assessment](#) published to accompany the 5-year
13 strategy aimed to support the introduction of the strategy and highlighted the importance of
14 preserving current effective therapies by focusing on the appropriate use of antimicrobials
15 (including using the correct antimicrobial, dose and duration of treatment for every
16 prescription, and using them wisely and sparingly). To further support the antimicrobial
17 resistance strategy more information is provided in the government's [antimicrobial resistance](#)
18 [collection](#).

19 **Resources for organisations and health professionals**

20 A number of resources have been published for organisations and health professionals with
21 the aim of improving the quality of antimicrobial prescribing and reducing the emergence of
22 resistance in different care settings.

23 In 2011 the Department of Health Advisory Committee on Antimicrobial Resistance and
24 Healthcare Associated Infection (ARHAI) published [Antimicrobial stewardship: Start](#)
25 [smart - then focus](#), which provides guidance for antimicrobial stewardship in hospitals in
26 England. The guidance stresses the importance of clear governance arrangements when
27 managing antimicrobial resistance.

28 The [TARGET toolkit](#) has been developed by the Royal College of General Practitioners
29 (RCGP), Public Health England (PHE) and The Antimicrobial Stewardship in Primary Care
30 (ASPIC) in collaboration with professional societies, as a central resource for health
31 professionals and commissioners about safe, effective, appropriate and responsible antibiotic
32 prescribing.

33 In 2013 the Department of Health and PHE published [antimicrobial prescribing and](#)
34 [stewardship competencies](#), which aim to improve the quality of antimicrobial treatment and
35 stewardship, and so reduce the risks and ill-effects of inadequate and inappropriate
36 treatment.

37 PHE has also published guidance on:

- 38 • [Primary care guidance: diagnosing and managing infections](#) (2013)
- 39 • [Managing common infections: guidance for consultation and adaptation](#) (2014)
- 40 • [Carbapenemase-producing Enterobacteriaceae: early detection, management and control](#)
41 [toolkit for acute trusts](#) (2014).

42 **National prescribing data**

43 Antimicrobial prescribing data are available through the [Health and Social Care Information](#)
44 [Centre](#) (HSCIC). The data report monthly GP practice prescribing and provide annual reports

1 on prescribing by dentists. The [NHS Business Services Authority](#) (NHS BSA) processes all
2 prescriptions dispensed in England in the community setting and collates prescribing data,
3 which can be analysed down to individual prescriber level. Furthermore, the [Department for
4 Environment, Food and Rural Affairs](#) (DEFRA) is reviewing antibiotic use in both humans and
5 animals as a marker of their actions to reduce use.
6

7 **1.2 Legal framework**

8 **1.2.1 Regulatory requirements**

9 The [Care Quality Commission](#) (CQC) is the regulatory body for hospitals, adult care homes,
10 dental and GP surgeries and all other care services in England.

11 In the [Essential standards of quality and safety](#) (2010) the CQC sets out what providers
12 should do to comply with the [section 20 regulations](#) of the Health and Social Care Act 2008.
13 Outcome 8 of the standards covers cleanliness and infection control and relates to
14 compliance with [Regulation 12](#) of the Health and Social Care Act 2008 (Regulated Activities)
15 Regulations 2010.

16 Guidance for providers on compliance with Regulation 12 is issued by the Department of
17 Health in [The Health and Social Care Act 2008: Code of Practice on the prevention and
18 control of infections and related guidance](#) (2010, updated 2011). The 'Code of Practice' sets
19 out '10 criteria against which a registered provider will be judged on how it complies with the
20 registration requirement for cleanliness and infection control' (Department of Health 2010). In
21 'part 3: guidance for compliance', criterion 9 outlines the processes that should be in place to
22 ensure prudent prescribing and antimicrobial stewardship. It suggests that there should be
23 an ongoing programme of audit, revision and update. In healthcare this is usually monitored
24 by an antimicrobial management team or local prescribing advisors.

25 **Children's care homes**

26 Children's care homes in England are regulated by the Office for Standards in Education,
27 Children's Services and Skills (Ofsted). The [Children's Homes Regulations 2001](#) and the
28 accompanying [Children's Homes: National Minimum Standards](#) (Department for Education
29 2011) do not specifically cover antimicrobial stewardship processes. However the National
30 Minimum Standards (2011) document does require (standard 6.7) that 'staff have received
31 sufficient training on health and hygiene issues and first aid with particular emphasis on
32 health promotion and communicable diseases'.

33 **1.3 Definitions used in the guideline**

34 **Antimicrobial stewardship**

35 The term 'antimicrobial stewardship' is defined as an approach that 'embodies an
36 organisational or healthcare-system-wide approach to promoting and monitoring judicious
37 use of antimicrobials to preserve their future effectiveness' as in the [annual report of the
38 Chief Medical Officer, volume two, 2011: Infections and the rise of antimicrobial resistance](#).

- 1 **Antimicrobial resistance**
- 2 The term ‘antimicrobial resistance’ is defined according to the [Executive Board of the World](#)
3 [Health Organization](#) (WHO) as the ‘loss of effectiveness of any anti-infective medicine,
4 including antiviral, antifungal, antibacterial and antiparasitic medicines’.
- 5 **Antimicrobial or antimicrobial medicine**
- 6 The term ‘antimicrobials’ and ‘antimicrobial medicines’ includes all anti-infective therapies
7 (antiviral, antifungal, antibacterial and antiparasitic medicines), and all formulations (oral,
8 parenteral and topical agents).
- 9 **Organisations**
- 10 The term 'organisations' is used to include all commissioners and providers, unless specified
11 otherwise in the text.
- 12 Commissioners are those individuals who undertake commissioning which is 'the process
13 used by health services and local authorities to: identify the need for local services; assess
14 this need against the services and resources available from public, private and voluntary
15 organisations; decide priorities; and set up contracts and service agreements to buy
16 services. As part of the commissioning process, services are regularly evaluated'.
- 17 Providers are organisations that directly provide health or social care services to people
18 (such as social enterprises, dentists, GPs, out-of-hours services, hospitals). Where the
19 guideline needs to distinguish hospital care from care provided in the community the terms
20 secondary care and primary care are used respectively.
- 21 **Health and social care practitioners**
- 22 The term 'health and social care practitioners' is used to define the wider care team,
23 including but not limited to, case managers, care coordinators, GPs, hospital doctors,
24 microbiologists, pharmacists, nurses and social workers. When specific recommendations
25 are made for a particular professional group, this is specified in the recommendation.
- 26 **Local decision-making groups**
- 27 Local decision-making groups include area prescribing committees, drug and therapeutics
28 committees, commissioner-based prioritisation groups, and clinical networks that are
29 responsible for making decisions on behalf of a local health and/or social care organisation.
- 30 Other definitions used in this guideline are given in the [glossary](#).
- 31 **1.4 Person-centred care**
- 32 This guideline offers best practice advice on the effective use of antimicrobial medicines.
- 33 Patients and health professionals have rights and responsibilities as set out in the [NHS](#)
34 [Constitution for England](#) – all NICE guidance is written to reflect these. Treatment and care
35 should take into account individual needs and preferences. Patients should have the
36 opportunity to make informed decisions about their care and treatment, in partnership with
37 their health professionals. If the person is under 16, their family or carers should also be
38 given information and support to help the child or young person to make decisions about
39 their treatment. Health professionals should follow the [Department of Health's advice on](#)
40 [consent](#). If a person does not have capacity to make decisions, health and social care

1 practitioners should follow the [code of practice that accompanies the Mental Capacity Act](#)
2 and the supplementary [code of practice on deprivation of liberty safeguards](#).

3 NICE has produced guidance on the components of good patient experience in adult NHS
4 services. All health professionals should follow the recommendations in [Patient experience in](#)
5 [adult NHS services](#). In addition, all health and social care practitioners working with people
6 using adult NHS mental health services should follow the recommendations in [Service user](#)
7 [experience in adult mental health](#). If a young person is moving between paediatric and adult
8 services, care should be planned and managed according to the best practice guidance
9 described in the Department of Health's [Transition: getting it right for young people](#). Adult
10 and paediatric healthcare teams should work jointly to provide assessment and services to
11 young people and diagnosis and management should be reviewed throughout the transition
12 process. There should be clarity about who is the lead clinician to ensure continuity of care.

13 **1.5 Strength of recommendations**

14 Some recommendations can be made with more certainty than others, depending on the
15 quality of the underpinning evidence. The Guideline Development Group (GDG) makes a
16 recommendation based on the trade-off between the benefits and harms of an intervention,
17 taking into account the quality of the underpinning evidence. The wording used in the
18 recommendations in this guideline denotes the certainty with which the recommendation is
19 made (the strength of the recommendation).

20 For all recommendations, NICE expects that there is discussion with the person about the
21 risks and benefits of the interventions, and their values and preferences. This discussion
22 aims to help them to reach a fully informed decision (see also '[Person-centred care](#)').

23 **1.5.1 Recommendations using 'should' (or 'should not') – 'strong' recommendations**

24 For recommendations using 'should' (or 'should not') the GDG was confident to recommend
25 the course of action.

26 **1.5.2 Recommendations using 'should consider'**

27 For recommendations using 'should consider' the GDG was less confident to recommend the
28 course of action than for a recommendation using 'should' or 'should not'.

29

30

31

2 Development of a NICE guideline

2.1 What is a NICE medicines practice guideline?

NICE guidelines make evidence-based recommendations on a wide range of topics, from preventing and managing specific conditions, improving health and managing medicines in different settings, to providing social care to adults and children, and planning broader services and interventions to improve the health of communities.

NICE guidelines cover health and social care in England and use the best available evidence; they involve people affected by the guideline and advance equality of opportunity for people who share characteristics protected under the Equality Act (2010).

In addition to the recommendations, guidelines also summarise the evidence behind the recommendations and explain how the recommendations were derived from the evidence. Many guideline recommendations are for individual health and social care practitioners, who should use them in their work in conjunction with judgement and discussion with people using services. Some recommendations are for local authorities, commissioners and managers, and cover planning, commissioning and improving services. Health professionals should take NICE guidance fully into account when exercising their clinical judgement, but it does not override their responsibility to make decisions appropriate to the circumstances and wishes of the individual patient. The reasons for any differences should be documented.

Predetermined and systematic methods are used to identify and evaluate the evidence.

The guidelines are produced using the following steps:

- the guideline topic is referred to NICE from the Department of Health
- stakeholders register an interest in the guideline and are consulted throughout the development process
- the NICE prepares the scope (stakeholders can comment on the draft at a scoping workshop and through a 4-week consultation)
- the NICE establishes a Guideline Development Group (GDG) (through a formal application and selection process)
- a draft guideline is produced after the GDG assesses the available evidence and makes recommendations
- there is a consultation on the draft guideline
- the final guideline is published.

NICE produces a number of different versions of this guideline the:

- 'full guideline' contains all the recommendations, plus details of the methods used and the underpinning evidence
- 'short guideline' lists the recommendations
- 'information for the public' is a summary of the recommendations written in plain English for people without specialist medical knowledge
- 'NICE pathways' brings together all related NICE guidance.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk.

1 **2.2 Remit**

2 NICE received the remit for the guideline from the Department of Health and Public Health
3 England. The NICE Medicines and Prescribing Centre produced the guideline.

4 **2.3 Who developed the guideline**

5 A multidisciplinary Guideline Development Group (GDG) comprising health professionals and
6 lay members developed this guideline (see [The Guideline Development Group and NICE](#)
7 [project team](#) for more information).

8 The National Institute for Health and Care Excellence (NICE) supported the development of
9 this guideline. The GDG was convened by the NICE Medicines and Prescribing Centre and
10 was chaired by Professor Alastair Hay, in accordance with guidance from NICE.

11 The group met regularly during the development of the guideline. At the start of the guideline
12 development process all GDG members declared interests in line with the NICE [code of](#)
13 [practice on declaring and dealing with conflicts of interest](#), this included any consultancies,
14 fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all
15 subsequent GDG meetings, members declared arising conflicts of interest.

16 Members were either required to withdraw for all or for part of the discussion if their declared
17 interest made it appropriate to do so. The details of declared interests and the actions taken
18 are shown in appendix A.

19 Staff from the NICE Medicines and Prescribing Centre provided methodological support and
20 guidance for the development process. The team working on the guideline included an
21 assistant project manager, systematic reviewers (senior advisers), health economists,
22 information scientists and a project lead. They undertook systematic searches of the
23 literature, appraised the evidence, conducted meta-analysis and cost effectiveness analysis
24 where appropriate, and drafted the guideline in collaboration with the GDG.

25 **2.4 Purpose and audience**

26 The purpose of this guideline is to provide good practice recommendations on systems and
27 processes for the effective use of antimicrobials.

28 This guideline may be of interest to adults, young people and children (including neonates)
29 using antimicrobials or those caring for these groups. This includes people and organisations
30 involved with the prescribing and management of antimicrobials in health and social care
31 settings.

32 It is anticipated that health and social care providers and commissioners of services will need
33 to work together to ensure that patients benefit from the good practice recommendations in
34 this guideline.

35 This guidance may also be relevant to individual people and organisations delivering non-
36 NHS healthcare services, and to other devolved administrations.

37 **2.5 What this guideline covers**

38 The guideline covers:

- 39 • Health and social care practitioners (a term used to define the wider care team of hospital
40 staff [including microbiologists and infection control staff], community matrons and case

- 1 managers, GPs, pharmacists and community nurses [including those staff working in out-
2 of-hours services], domiciliary care workers and care home staff [registered nurses and
3 social care practitioners working in care homes], social workers and case managers).
- 4 • Organisations commissioning (for example, clinical commissioning groups or local
5 authorities), providing or supporting the provision of care (for example, national or
6 professional bodies, directors of public health, health and wellbeing boards, healthcare
7 trusts and locum agencies).
 - 8 • Adults, young people and children (including neonates) using antimicrobials, or those
9 caring for these groups.
- 10 Settings covered include:
- 11 • All publicly funded health and social care commissioned or provided by NHS
12 organisations, local authorities (in England), independent organisations or independent
13 contractors.
- 14 This guideline may also be relevant to individual people and organisations delivering non-
15 NHS healthcare services, and to other devolved administrations.
- 16 For further details please refer to the scope in appendix B and review questions in appendix
17 C.2.

18 **2.6 What this guideline does not cover**

- 19 The guideline does not cover:
- 20 • specific clinical conditions (although some evidence identified included patients with a
21 specific infection such as community acquired pneumonia)
 - 22 • named medicines
 - 23 • public health awareness of antimicrobial resistance
 - 24 • research into new antimicrobials
 - 25 • immunisation and vaccination
 - 26 • antimicrobial household cleaning products
 - 27 • antimicrobial use in animals
 - 28 • hand hygiene, decolonisation and infection prevention and control measures
 - 29 • medicines adherence, except where there are specific issues for health and social care
30 practitioners to address relating to antimicrobials
 - 31 • access to medicines, including local decision-making for medicines not included on local
32 formularies
 - 33 • medicines shortages, including supply issues and discontinued medicines
 - 34 • prescription charges
 - 35 • waste medicines.

36 **2.7 Related NICE guidance**

37 **2.7.1 Published**

- 38 • [Pneumonia](#). NICE guideline CG191 (2014).
- 39 • [Drug allergy](#). NICE guideline CG183 (2014).
- 40 • [Managing medicines in care homes](#). NICE guideline SC1 (2014).

- 1 • [Patient group directions](#). NICE guideline MPG2 (2013).
- 2 • [Infection](#). NICE guideline CG139 (2012).
- 3 • [Patient experience in adult NHS services](#). NICE guideline CG138 (2012).
- 4 • [Developing and updating local formularies](#). NICE guideline MPG1 (2012).
- 5 • [Service user experience in adult mental health](#). NICE guideline CG136 (2011).
- 6 • [Prevention and control of healthcare-associated infections](#) NICE guideline PH36 (2011).
- 7 • [Medicines adherence](#). NICE guideline CG76 (2009).
- 8 • [Surgical site infection](#). NICE guideline CG74 (2008).
- 9 • [Respiratory tract infections – antibiotic prescribing](#) NICE guideline CG69 (2008).

10 2.7.2 Under development

- 11 NICE is currently developing the following related guidance (details available from the NICE
12 website):
- 13 • [Medicines optimisation](#). NICE guideline. Publication expected March 2015.
 - 14 • [Antimicrobial resistance: changing risk-related behaviours](#). NICE guideline. Publication
15 expected March 2016.

3 Methods

This chapter sets out in detail the methods used to review the evidence and to generate the recommendations ([see section 4.2](#)). This guideline was developed in accordance with the methods outlined in the [Interim methods guide for developing good practice guidance 2013](#). From February 2014, good practice guidance became known as medicines practice guidelines. This is to bring the guideline naming in line with other NICE products. This is purely a name change, the processes and methods used to develop the guidelines remain the same.

At the start of guideline development, the key issues listed in the scope were translated into review questions. Each review question in this guideline is presented in a separate section. Each section includes:

- clinical evidence review
- health economic evidence
- evidence statements
- evidence to recommendations
- recommendations and research recommendations.

Additional information is provided in the appendices for each review question and includes:

- evidence tables
- GRADE profiles (as appropriate)
- Forest plots (as appropriate).

A call for evidence was used for the review question relating to the timely adoption and diffusion of a new antimicrobial. A call for written evidence can be used if the GDG and NICE project team agree that information exists that has not been found using standard searches (as outlined in section 8.9 of the [Interim methods guide for developing good practice guidance](#)).

3.1 Developing review questions and outcomes

3.1.1 Review questions

Review questions were developed in a PICO (patient, intervention, comparison and outcome) format and intervention reviews were carried out. For each review question, a review protocol was developed. The review protocols then informed the literature search strategy for each review question. The methods used are detailed fully in section 7 of the [Interim methods guide for developing good practice guidance](#).

During the scoping phase 3 review questions were identified. These were all questions to identify the effectiveness and cost effectiveness of interventions. In line with the Interim methods guide for developing good practice guidance, review questions relating to interventions are usually best answered by randomised controlled trials (RCTs), because this is most likely to give an unbiased estimate of the effects of an intervention.

The GDG discussed the draft review questions at GDG meetings and agreed that minor changes were needed to several outlined in the final scope document (see table 1). Following the scoping phase, an additional review question was identified and is included in the guideline. The need for the review questions was discussed and agreed by the GDG.

1 **Table 1: Summary of changes made to review questions from the final scope**

Review question wording in scope	Final review question
What systems and processes are effective and cost-effective in reducing the emergence of antimicrobial resistance without causing additional harm to patients?	What interventions, systems and processes are effective and cost-effective in reducing antimicrobial resistance without causing harm to patients?
What interventions, systems and processes are effective and cost-effective in changing health and social care practitioners' decision making to ensure appropriate antimicrobial stewardship?	No change
What interventions, systems and processes are effective in overcoming the barriers to decision making by health and social care practitioners when ensuring appropriate antimicrobial stewardship?	What interventions, systems and processes are effective and cost-effective in overcoming the barriers to decision making by health and social care practitioners when ensuring appropriate antimicrobial stewardship?
Additional review question agreed by the GDG	What interventions, systems and processes are effective and cost-effective in the responsible, timely adoption and diffusion, where appropriate, of a 'new' antimicrobial into the National Health Service?

2 **3.1.2 Writing the review protocols**

3 For each review question a review protocol was developed in accordance with section 7 of
 4 the [Interim methods guide for developing good practice guidance](#); the final review protocols
 5 can be found in appendix C.2

6 Review protocols outline the background, the objectives and planned methods to be used to
 7 undertake the review of evidence to answer the review question. They explain how each
 8 review is to be carried out and help the reviewer plan and think about different stages. They
 9 also provide some protection against the introduction of bias and allow for the review to be
 10 repeated by others at a later date.

11 Each review protocol includes:

- 12 • the review question
- 13 • objectives
- 14 • type of review
- 15 • language
- 16 • study design
- 17 • status
- 18 • population
- 19 • intervention
- 20 • comparator
- 21 • outcomes
- 22 • other criteria for inclusion/exclusion of studies
- 23 • search strategies
- 24 • review strategies
- 25 • identified papers from the scoping search for background, including relevant legislation
 26 (UK) or national policy
- 27 • identified papers from the scoping search that address the review question.

1 In addition, for each review protocol the GDG considered how any equality issues could be
2 addressed in planning the review work.

3 Each review protocol was discussed and agreed by the GDG. This included the GDG
4 agreeing the critical and important outcomes for each review question. These are shown in
5 the review protocols.

6 **3.2 Searching for evidence**

7 **3.2.1 Clinical and health economic literature searching**

8 Scoping searches were undertaken in January 2014 to identify previous clinical guidelines,
9 health technology assessment reports, key systematic reviews and economic evaluations
10 relevant to the topic.

11 Systematic literature searches were carried out by an information specialist in the NICE
12 guidance information services between June and October 2014 to identify all published
13 clinical evidence relevant to the review questions. Searches were carried out according to
14 the methods in section 7 of the [Interim methods guide for developing good practice
15 guidance](#).

16 Databases were searched using relevant medical subject headings and free-text terms.
17 Where relevant, searches were restricted to systematic reviews and RCTs. Studies
18 published in languages other than English were not reviewed and the searches were not
19 date restricted. The following databases were searched for all questions: Cochrane
20 Database of Systematic Reviews (CDSR), HTA Database, Database of Abstracts of Reviews
21 of Effects (DARE), MEDLINE, Embase, the Cochrane library, NHS Economic Evaluation
22 Database (NHS EED) and Health Economic Evaluations Database (HEED).

23 The clinical and economic evidence search strategies can be found in appendix C.1

24 **3.3 Reviewing the evidence**

25 The evidence retrieved from the search strategy was systematically reviewed for each review
26 protocol. Evidence identified from the literature search was reviewed by title and abstract
27 (first sift). Those studies not meeting the inclusion criteria were excluded. Full papers of the
28 included studies were requested. All full-text papers were then reviewed and those studies
29 not meeting the inclusion criteria were excluded (second sift). Relevant data from each
30 included study were extracted and included in the 'Summary of included studies' table.
31 These tables can be found in the relevant 'Evidence review' section. An overview of the
32 systematic review process followed is detailed in section 8 of the [Interim methods guide for
33 developing good practice guidance](#).

34 **3.3.1 Inclusion and exclusion criteria**

35 Selection of relevant studies was carried out by applying the inclusion and exclusion criteria
36 listed in the review protocols (see appendix C.2). All excluded studies and reasons for their
37 exclusion can be found in appendices C.5 and C.6. Included studies were agreed with the
38 GDG.

39 **3.3.2 Methods of combining clinical studies**

40 Where possible, a meta-analysis was carried out to combine the results of studies for each
41 review question using Cochrane Review Manager (RevMan5) software. However, because

1 many different interventions were considered, a meta-analysis was only possible for the
2 review questions on reducing antimicrobial resistance and decision-making.

3 3.3.3 Types of studies

4 Only evidence in the English language was considered. For all review questions the following
5 types of studies were considered in the reviews:

- 6 • Systematic reviews of RCTs.
- 7 • RCTs.
- 8 • For questions on barriers to decision-making and timely adoption and diffusion of a new
9 antimicrobial, qualitative studies and cross-sectional surveys were included in the
10 absence of any RCT evidence.

11 Systematic reviews of RCTs were only included in their entirety if all RCTs met the criteria
12 listed in the review protocol. When this was not the case, relevant RCTs included in the
13 systematic review were identified and included. Conference abstracts were not considered
14 as part of the review because higher quality evidence was identified for each question.

15 Characteristics of data from included studies were extracted into a standard template for
16 inclusion in an evidence table, which can be found in appendix D.1. Evidence tables help to
17 identify the similarities and differences between studies, including the key characteristics of
18 the study population and interventions or outcome measures. This provides a basis for
19 comparison.

20 3.3.4 Call for evidence

21 Following the review of the published literature, the NICE project team (in consultation with
22 the GDG) may consider that there is insufficient published evidence. This gap in evidence
23 can be appropriately supplemented through a call for evidence. Therefore for the review
24 question relating to the timely adoption and diffusion of a new antimicrobial, a call for
25 evidence was undertaken. The methods for this were in line with section 8 of the Interim
26 Methods Guide for Developing Good Practice Guidance. An email, with questions agreed by
27 the GDG, was sent to all of those who had registered for news and updates from the
28 Medicines and Prescribing Centre and all stakeholders registered for this guideline.

29 3.3.5 Appraising the quality of evidence by outcomes

30 Evidence was appraised for outcomes identified from included RCTs and, where appropriate,
31 observational studies. These studies were assessed using the appropriate methodology
32 checklists as per [Developing NICE guidelines: the manual](#) (2014). The 'Grading of
33 Recommendations Assessment, Development and Evaluation (GRADE)' approach to
34 assessing the quality of evidence where this was possible. [Developing NICE guidelines: the
35 manual](#) (2014) explains that 'GRADE is a system developed by an international working
36 group for rating the quality of evidence across outcomes in systematic reviews and
37 guidelines. The system is designed for reviews and guidelines that examine alternative
38 management strategies or interventions, and these may include no intervention or current
39 best management. Results of the analysis were presented in 'GRADE profiles' (see appendix
40 D.2 for all GRADE profiles).

41 The evidence for each outcome was examined separately for the quality elements listed and
42 defined in table 2. Each element was graded using the quality levels listed in table 3. The
43 main criteria considered in the rating of these elements are discussed below. Footnotes were
44 used to describe reasons for grading a quality element as having serious or very serious

1 problems. The ratings for each component were summed to obtain an overall quality
 2 assessment for each outcome (table 4).

3 **Table 2: Description of the elements in GRADE used to assess the quality of**
 4 **intervention studies**

Quality element	Description
Study limitations (risk of bias)	The internal validity of the evidence
Inconsistency	The heterogeneity or variability in estimates of treatment effect across studies
Indirectness	The degree of differences between the population, intervention, comparator for the intervention and outcome of interest across studies
Imprecision (random error)	The extent to which confidence in the effect estimate is adequate to support a particular decision
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies

5 **Table 3: Levels of quality elements in GRADE**

Level	Description
None/no serious	There are no serious issues with the evidence
Serious	The issues are serious enough to downgrade the outcome evidence by 1 level
Very serious	The issues are serious enough to downgrade the outcome evidence by 2 levels

6 **Table 4: Overall quality of outcome evidence in GRADE**

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

7 For the evidence included in the question on ‘barriers to decision-making’ (qualitative and
 8 cross-sectional studies), the GRADE framework was not considered appropriate. The
 9 qualitative studies were assessed using the NICE methodology checklist for qualitative
 10 studies (see [the Guidelines manual – Appendix H](#) [2012]). A checklist originally published in
 11 the [British Medical Journal](#) was used to aid in the quality assessment of the cross-sectional
 12 surveys.

13 **3.3.6 Evidence statements (summarising and presenting results for effectiveness)**

14 Evidence statements for outcomes were developed to include a summary of the key features
 15 of the evidence. For each question, evidence statements for clinical and cost effectiveness
 16 were summaries of the evidence. These were produced to support the GDG in their review of
 17 the evidence and decision-making when linking evidence to recommendations. The wording
 18 of the statement reflects the certainty or uncertainty in the estimate of effect.

1 **3.4 Evidence of cost effectiveness**

2 The GDG needs to make recommendations based on the best available evidence of clinical
3 and cost effectiveness. Guideline recommendations should be based on the estimated costs
4 of the interventions or services in relation to their expected health benefits (that is, their 'cost
5 effectiveness'), rather than on the total cost or resource impact of implementing them. Thus,
6 if the evidence suggests that an intervention or service provides significant health benefits at
7 an acceptable cost per patient treated, it should be recommended even if it would be
8 expensive to implement across the whole population.

9 Evidence on cost effectiveness related to the key clinical issues addressed in the guideline
10 was sought. The health economist undertook a systematic review of the published economic
11 literature (see appendix C.1.3 and C.4 for details of the searches and search results),
12 including critical appraisal of relevant studies using the economic evaluations checklist as
13 specified in appendix H of [Developing NICE guidelines: the manual](#) (2014).

14 **3.5 Developing recommendations**

15 The GDG reviewed the evidence of clinical and cost effectiveness in the context of each of
16 the 4 review questions to develop recommendations that would provide national guidance
17 and advice to health and social care practitioners and commissioning and provider
18 organisations.

19 The recommendations were drafted based on the GDG's interpretation of the evidence
20 presented, where they considered the relative values of different outcomes, trade-offs
21 between benefits and harms, quality of the evidence, costs of different interventions and
22 other factors they may need to be consider in relation to the intervention.

23 For each review question the clinical effectiveness evidence was presented first, considering
24 the net benefit over harm for the prioritised critical outcomes (as set out in the review
25 protocols [see appendix C.2]). This involved an informal discussion, details of which are
26 captured in the 'Evidence to recommendations' table for each review question.

27 The GDG then reviewed any cost effectiveness evidence and considered how this impacted
28 on the decisions made after presentation of the clinical and cost effectiveness evidence. The
29 recommendation wording considered the quality of the evidence and the confidence the
30 GDG had in the evidence that was presented, in addition to the importance of the prioritised
31 outcomes (the GDG's values and preferences).

32 Where clinical or cost effectiveness evidence was of poor quality, conflicting or absent, the
33 GDG drafted recommendations based on their expert opinion. Consensus based
34 recommendations considered the balance between potential benefits and harms; economic
35 costs compared with benefits, current practice, other guideline recommendations, patient
36 preferences and equality issues and were agreed through discussion with the GDG.

37 The wording of the recommendations took into account the strength of the evidence and
38 wording was based on section 9 of [Developing NICE guidelines: the manual](#) (2014)
39 principles. Some recommendations are strong in that the GDG believes that the vast majority
40 of health and other professionals and people would choose a particular intervention if they
41 considered the evidence in the same way that the GDG has. This is generally the case if the
42 benefits of an intervention outweigh the harms for most people and the intervention is likely
43 to be cost effective. Where the balance between benefit and harm is less clear cut, then the
44 recommendations are 'weaker'; some people may not choose an intervention, whereas
45 others would.

1 See section 9 of [Developing NICE guidelines: the manual](#) (2014) or more information on
2 developing and wording recommendations.

3 **3.6 Research recommendations**

4 When areas were identified for which good evidence was lacking, the GDG considered
5 making recommendations for future research. Decisions about inclusion were based on
6 factors such as:

- 7 • the importance to patients or the population
- 8 • national priorities
- 9 • potential impact on the NHS and future NICE guidance
- 10 • ethical and technical feasibility.

11 **3.7 Validation review**

12 **3.7.1 Validation process**

13 This guideline is subject to a 4-week public consultation. This allows stakeholders, members
14 of the public and other NICE teams to peer review the document as part of the quality
15 assurance process. All comments received from registered stakeholders within the specified
16 deadline will be responded to. All comments received and responses given will be posted on
17 the NICE website.

18 **3.7.2 Updating the guideline**

19 The guideline will be updated in accordance with the process outlined in section 14 of
20 [Developing NICE guidelines: the manual](#) (2014).

21 **3.7.3 Disclaimer**

22 This guideline represents the views of NICE and was arrived at after careful consideration of
23 the evidence available. Those working in the NHS, local authorities, the wider public,
24 voluntary and community sectors and the private sector should take it into account when
25 carrying out their professional, managerial or voluntary duties.

26 Implementation of this guidance is the responsibility of local commissioners and/or providers.
27 Commissioners and providers are reminded that it is their responsibility to implement the
28 guidance, in their local context, in light of their duties to have due regard to the need to
29 eliminate unlawful discrimination, advance equality of opportunity and foster good relations.
30 Nothing in this guidance should be interpreted in a way that would be inconsistent with
31 compliance with those duties.

32 **3.7.4 Funding**

33 NICE commissioned the NICE Medicines and Prescribing Centre to produce this guideline.

4 Guideline summary

4.1 Implementation section

During consultation we want you to let us know of up to 3 recommendations or areas of the guideline that you think will be challenging to put into practice. Please tell us for whom and why. We would also like you to send us suggestions of ways that you think these challenges could be addressed – such as by sharing examples of good practice or by letting us know about existing educational materials or other resources. This information will be used to write an implementation section for the final guideline.

Please send us your comments and suggestions using the comments form.

4.2 Full list of recommendations

All antimicrobials

Recommendations for organisations (commissioners and providers)

Antimicrobial stewardship programmes

1. **Organisations should establish an antimicrobial stewardship programme, taking account of the resources needed to support antimicrobial stewardship across all care settings.**
2. **Organisations should consider including the following in an antimicrobial stewardship programme:**
 - monitoring and evaluating antimicrobial prescribing and how this relates to local resistance patterns
 - providing regular feedback to prescribers in all care settings about:
 - their antimicrobial prescribing, for example, by using professional regulatory numbers for prescribing as well as prescriber (cost centre) codes
 - patient safety incidents related to antimicrobials, including hospital admissions for rare or serious infections or associated complications
 - providing education and training to health and social care practitioners about antimicrobial stewardship and antimicrobial resistance.
3. **Organisations should clearly define roles, responsibilities and accountability within an antimicrobial stewardship programme.**
4. **Organisations should consider developing systems and processes for providing regular updates (at least every year) to individual prescribers and prescribing leads on:**
 - national and local antimicrobial prescribing patterns
 - local antimicrobial resistance patterns
 - patient safety incident patterns relating to antimicrobial use.

1 **5. Organisations should consider developing systems and processes for identifying**
2 **and reviewing previous and current antimicrobial prescribing for patients who are**
3 **admitted to hospital with severe infections.**

4 *Antimicrobial stewardship interventions*

5 **6. Organisations should consider using the following antimicrobial stewardship**
6 **interventions:**

- 7 • review of prescribing by antimicrobial stewardship teams and promotion
8 of appropriate antimicrobial use
- 9 • IT or decision support systems
- 10 • education-based programmes for health and social care practitioners
11 (for example, academic detailing, clinical education or educational
12 outreach).

13 **7. Organisations should consider providing IT or decision support systems that**
14 **prescribers can use to decide:**

- 15 • whether to prescribe an antimicrobial or not, particularly when
16 antimicrobials are frequently prescribed for a condition but may not be
17 the best option
- 18 • whether alternatives to immediate antimicrobial prescribing (such as
19 delayed prescribing or early review if concerns arise) may be
20 appropriate.

21 **8. When developing care pathways, organisations should consider including:**

- 22 • information about antimicrobial use
- 23 • advice about who a patient should contact if they have concerns about
24 infection after discharge from secondary care.

25 **9. Organisations should consider prioritising the monitoring of antimicrobial**
26 **resistance, to support antimicrobial stewardship across all care settings, taking**
27 **into account the resources and programmes needed.**

28 **10. Organisations should stock antimicrobials in pack sizes that correspond to local**
29 **guidelines on course lengths.**

30 **11. Organisations should consider evaluating the effectiveness of antimicrobial**
31 **stewardship interventions by reviewing antimicrobial prescribing and resistance**
32 **patterns.**

33 **12. Organisations should provide feedback to prescribers on their antimicrobial**
34 **prescribing.**

35 *Antimicrobial stewardship teams*

36 **13. Organisations should establish an antimicrobial stewardship team that operates**
37 **across all care settings as part of the antimicrobial stewardship programme. The**
38 **team should have core members and may co-opt additional members depending**
39 **on the setting and antimicrobial issue being considered.**

1 **14. Organisations should support the antimicrobial stewardship team to:**

- 2 • review prescribing and resistance data and identify ways of feeding this
3 information back to prescribers in all care settings.
- 4 • provide education to prescribers in all care settings
- 5 • assist the local formulary decision-making group with recommendations
6 about new antimicrobials
- 7 • update local formulary and prescribing guidance
- 8 • work with prescribers to investigate the reasons for very high, increasing
9 or very low volumes of antimicrobial prescribing, or inappropriate
10 antimicrobial use
- 11 • provide feedback and assistance to prescribers who prescribe
12 antimicrobials outside of local guidelines where it is not justified.

13 *Communication*

14 **15. Organisations should encourage and support prescribers only to prescribe**
15 **antimicrobials when this is clinically appropriate.**

16 **16. Organisations should encourage health and social care practitioners across all**
17 **care settings to work together to support antimicrobial stewardship by:**

- 18 • communicating and sharing consistent messages about antimicrobial
19 use
- 20 • sharing learning and experiences about antimicrobial resistance and
21 stewardship
- 22 • referring appropriately between services without raising expectations
23 that antimicrobials will subsequently be prescribed.

24 **17. Organisations should consider developing local networks across all care settings**
25 **to communicate information and share learning on:**

- 26 • antimicrobial prescribing
- 27 • antimicrobial resistance
- 28 • patient safety incident patterns.

29 **18. Organisations should consider developing local systems and processes for peer**
30 **review of prescribing. They should encourage an open and transparent culture**
31 **that allows health professionals to question antimicrobial prescribing practices of**
32 **colleagues when these are not in line with local and national guidelines and no**
33 **reason is documented.**

34 **19. Organisations should encourage senior health professionals to promote**
35 **antimicrobial stewardship within their teams, recognising the influence that senior**
36 **prescribers can have on prescribing practices of colleagues.**

37 *Antimicrobial guidelines*

38 **20. Organisations should involve lead health and social care practitioners in**
39 **establishing processes for developing, reviewing, updating and implementing**
40 **local antimicrobial guidelines in line with national guidance and supported by**
41 **local prescribing data and resistance patterns.**

1 **21. Organisations should raise awareness of current local guidelines on antimicrobial**
2 **prescribing among all prescribers, providing updates if the guidelines change.**

3 *Laboratory testing*

4 **22. Organisations should ensure that laboratory testing and the order in which the**
5 **susceptibility of organisms to antimicrobials is reported is in line with:**

- 6 • national and local treatment guidelines
7 • the choice of antimicrobial in the local formulary
8 • the priorities of medicines management and antimicrobial stewardship
9 teams.

10 **Recommendations for prescribers**

11 *Antimicrobial stewardship*

12 **23. Prescribers should take into account the likely impact on antimicrobial resistance**
13 **when deciding whether or not to prescribe an antimicrobial.**

14 *Antimicrobial guidelines*

15 **24. Health and social care practitioners should support the implementation of local**
16 **antimicrobial guidelines and recognise their importance for antimicrobial**
17 **stewardship.**

18 **25. Prescribers should follow local guidelines when prescribing antimicrobials and**
19 **consider prescribing the shortest effective course at the most appropriate dose**
20 **for the individual patient.**

21 *Antimicrobial prescribing*

22 **26. Prescribers should undertake a clinical assessment and document the clinical**
23 **diagnosis (including symptoms) in the patient's record and clinical management**
24 **plan when prescribing any antimicrobial.**

25 **27. Prescribers should consider obtaining microbiological cultures before deciding**
26 **whether to prescribe an antimicrobial for a non-severe infection, providing it is**
27 **safe to withhold treatment until the results are available.**

28 **28. Prescribers should consider point of care testing in primary care as described in**
29 **the NICE guideline on [pneumonia](#).**

30 **29. Prescribers should take time to discuss with the patient and/or their family**
31 **members or carers (as appropriate):**

- 32 • the likely nature of the condition
33 • why prescribing an antimicrobial may not be the best option
34 • alternative options to prescribing an antimicrobial
35 • their views on antimicrobials, taking into account their priorities or
36 concerns for their current illness and whether they want or expect an
37 antimicrobial

- 1
- the benefits and harms of immediate antimicrobial prescribing
- 2
- what they should do if their condition deteriorates (safety netting advice),
- 3
- including providing any written information about this as appropriate.

4 **30. Prescribers should document in the patient’s records (electronically wherever**
5 **possible):**

- 6
- when an antimicrobial is prescribed
- 7
- the reason for prescribing, or not prescribing, an antimicrobial
- 8
- the plan of care as discussed with the patient, their family member or
- 9
- carer (as appropriate).

10 **31. Prescribers should not issue an immediate prescription for an antimicrobial to a**
11 **patient who is likely to have a self-limiting condition.**

12 **32. If immediate antimicrobial prescribing is not the most appropriate option,**
13 **prescribers should discuss with the patient and/or their family members or carers**
14 **(as appropriate) other options such as:**

- 15
- self-care with over-the-counter preparations
- 16
- delayed prescribing
- 17
- other non-pharmacological interventions, for example, draining the site
- 18
- of infection.

19 **33. When a decision to prescribe an antimicrobial has been made, prescribers should**
20 **take into account the benefits and harms for an individual patient associated with**
21 **the particular antimicrobial, including:**

- 22
- the risk of antimicrobial resistance
- 23
- possible interactions with other medicines
- 24
- the patient’s other illnesses, for example, the need for dose adjustment
- 25
- in a patient with renal impairment
- 26
- any drug allergies (these should be documented in the patient’s record)
- 27
- the risk of selection for organisms causing healthcare-associated
- 28
- infections, for example, *C. difficile*.

29 **34. When prescribing is outside national and local guidelines, prescribers should**
30 **consider documenting in the patient’s records the reasons for the decision.**

31 **35. Prescribers should not issue repeat prescriptions for antimicrobials for longer**
32 **than 6 months. A more frequent review may be needed for individual patients.**

33 *Prescribing intravenous antimicrobials*

34 **36. Prescribers should use an intravenous antibiotic from the agreed local formulary**
35 **and in line with local guidelines for a patient who needs an empirical intravenous**
36 **antimicrobial for a suspected infection but has no confirmed diagnosis.**

37 **37. Prescribers should consider reviewing intravenous antimicrobial prescriptions at**
38 **48–72 hours in all care settings (including community services) to determine if the**

1 antimicrobial needs to be continued, and if so whether the intravenous
2 antimicrobial can be switched to an oral antimicrobial.

3 **New antimicrobials**

4 **Recommendations for organisations (commissioners and providers)**

5 **38. Organisations should consider establishing processes for reviewing national**
6 **horizon scanning to plan for the release of new antimicrobials.**

7 **39. Organisations should consider using an existing local decision-making group (for**
8 **example, a drug and therapeutics committee, area prescribing committee or local**
9 **formulary decision-making group) to consider the introduction of new**
10 **antimicrobials locally. The group should include representatives from different**
11 **care settings and other local organisations to minimise the time to approval.**

12 **40. Organisations should consider using multiple approaches to support the**
13 **introduction of a new antimicrobial, including:**

- 14 • electronic alerts to notify prescribers about the antimicrobial
- 15 • prescribing guidance about when and where to use the antimicrobial in
16 practice
- 17 • issuing new or updated formulary guidelines and antimicrobial
18 prescribing guidelines
- 19 • peer advocacy and advice from other prescribers
- 20 • providing education or informal teaching on ward rounds
- 21 • shared risk management strategies for antimicrobials that are potentially
22 useful but may be associated with patient safety incidents.

23 **41. Once a new antimicrobial has been approved for local use, organisations should**
24 **consider ongoing monitoring by:**

- 25 • conducting an antimicrobial use review (reviewing whether prescribing is
26 appropriate and in line with the diagnosis and local and national
27 guidelines)
- 28 • costing the use of the new antimicrobial
- 29 • reviewing the use of non-formulary antimicrobial prescribing
- 30 • evaluating local prescribing and resistance patterns.

31 **Recommendations for local decision-making groups**

32 **42. Local decision-making groups should consider co-opting members with**
33 **appropriate expertise in antimicrobial stewardship when considering whether to**
34 **approve the introduction of a new antimicrobial locally, this may include those**
35 **involved in the antimicrobial stewardship team.**

36 **43. Local decision-making groups should ensure that local formularies, prescribing**
37 **guidelines and care pathways are updated when new antimicrobials are approved**
38 **for use.**

- 1 **44. When considering a new antimicrobial for local use and for inclusion in the local**
2 **formulary, local decision-making groups should take into account:**
3
 - 4 • the need for the new antimicrobial
 - 5 • the population in which it will be used
 - 6 • the specific organisms or conditions for which it will be used
 - 7 • dose, dose frequency, formulation and route of administration
 - 8 • likely tolerability and adherence
 - 9 • any drug interactions, contraindications or cautions
 - 10 • local patterns of resistance
 - 11 • whether use should be restricted and if so, how use will be monitored
 - 12 • any additional monitoring needed
 - 13 • any urgent clinical need for the new antimicrobial
 - 13 • any plans for introducing the new antimicrobial.

- 14 **45. Local decision-making groups should consider assessing the benefits and risks**
15 **of restricting access to a new antimicrobial.**

- 16 **46. Local decision-making groups should:**
17
 - 18 • document the rationale for restricting access to a new antimicrobial and
19 the nature of restriction, and ensure that this information is publically
20 available
 - 20 • review the restriction regularly to determine that it is still appropriate.

- 21 **47. Local decision-making groups should ensure that there is a plan for the timely**
22 **introduction, adoption and diffusion of a new antimicrobial when this has been**
23 **recommended for use.**

- 24 **48. Local decision-making groups should have discussions with commissioners early**
25 **in the approval process if funding concerns for a new antimicrobial are likely to**
26 **cause delay in its introduction, adoption and diffusion.**

- 27 **49. Local decision-making groups should indicate where prescribers can find**
28 **accurate, evidence-based and up-to-date information about the new**
29 **antimicrobial such as:**
30
 - 31 • the [electronic medicines compendium](#)
 - 32 • the [British National Formulary](#) (BNF)
 - 32 • the [British National Formulary for Children](#) (BNFC)
 - 33 • the [Medicines and Healthcare products Regulatory Agency](#) (MHRA).

34 **4.2.1 Research recommendations**

- 35 **1. One or more randomised controlled trials should be undertaken to determine**
36 **whether short versus longer courses of antimicrobials, directly administered (or**
37 **observed) therapy, continuous versus intermittent therapy and inhaled**
38 **antimicrobials reduce the emergence of resistance and maintain patient outcomes**
39 **compared with usual care in the UK setting.**

- 1
 - 2
 - 3
 - 4
- 2. Randomised controlled trials should be undertaken to determine whether use of point of care tests in decision-making is clinically and cost effective when prescribing antimicrobials in children, young people and adults presenting with respiratory tract infections.**

5 Reducing antimicrobial resistance

5.1 Introduction

Antimicrobial stewardship has been defined in the NICE quality standard on [infection prevention and control](#) (QS61) as ‘an organisational or healthcare-system-wide approach to promoting and monitoring judicious use of [antimicrobials] to preserve their future effectiveness’.

Antimicrobial resistance is not a new problem for healthcare and has been a global concern for many years. As resistance to antimicrobials grows the ability to successfully treat infections is reduced. Antimicrobial resistance can be defined as the ‘loss of effectiveness of any anti-infective medicine, including antiviral, antifungal, antibacterial and antiparasitic medicines’ ([World Health Organization](#) [WHO] 2014). The WHO’s 2014 [global report on surveillance](#) gives ‘as accurate a picture as is presently possible of the magnitude of [antimicrobial resistance] and the current state of surveillance globally’.

In 2011, the [annual report of the Chief Medical Officer, volume two, 2011: Infections and the rise of antimicrobial resistance](#) stated that 1 of the 3 major goals identified for antimicrobial stewardship is to ‘minimise the development of antimicrobial resistance at patient and community levels’. The Chief Medical Officer further stated that ‘firstly we need to preserve the effectiveness of our existing antimicrobial agents and secondly we need to encourage the development of new agents in the future. The key to preserving the effectiveness of our existing antimicrobial agents in England is better stewardship’.

In 2013, in response to this report, the Department of Health published a [5-year strategy for antimicrobial resistance](#), which aims to slow the development and spread of antimicrobial resistance. The strategy states that antimicrobial resistance cannot be eradicated, but by using a multidisciplinary approach, the risk of antimicrobial resistance can be limited and its impact on health now and in the future can be reduced. The report describes 3 strategic aims, 1 of which is to conserve and steward the effectiveness of existing treatments. An [impact assessment](#) has been carried out by the Department of Health alongside the 5-year strategy. This supports the introduction of the strategy and highlights issues such as the importance of preserving current effective therapies and focusing on the appropriate use of antimicrobials (including using the correct antimicrobial, dose and duration of treatment for every prescription, and using them wisely and sparingly). To further support the implementation of the 5-year strategy, the Department of Health and Public Health England have published a [competency framework for prescribers](#). The aim of this is to ‘improve the quality of antimicrobial treatment and stewardship and so reduce the risks of inadequate, inappropriate and ill-effects of treatment’.

To identify the prescribing trends for antimicrobials, in 2014 the English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) published a [report](#) reviewing prescribing patterns for antimicrobials in different care settings. It found that 79% of antimicrobial prescribing was from general practice (an increase of 4% between 2010 and 2013), 15% from hospitals (an increase of 12% between 2010 and 2013) and 6.2% was related to other community prescribers, predominantly dentists (an increase of 32% between 2010 and 2013). The report indicates that antimicrobial use is a major driver for the spread of antibiotic resistance. Resistant infections as a proportion of all infections remained stable from 2010 to 2013, but as the number of infections overall has increased so has the number of resistant infections.

The [Start smart - then focus](#) (Department of Health 2011) guidance was published ‘to provide an outline of evidence-based antimicrobial stewardship in the secondary healthcare setting’.

1 It covers the starting and reviewing of antimicrobial therapy in secondary care. Similarly the
2 [TARGET antibiotics toolkit](#) (Treat Antibiotics Responsibly, Guidance, Education, Tools) gives
3 guidance, educational material and tools for multidisciplinary primary care teams on the
4 issues of when and what antimicrobials to prescribe.

5 The NICE quality standard on [infection control and prevention](#) has a quality statement on
6 antimicrobial stewardship which expects that 'people are prescribed antibiotics in accordance
7 with local antibiotic formularies as part of antimicrobial stewardship'.

8 **Legislation and regulation**

9 The Care Quality Commission's (CQC) [Essential standards of quality and safety](#) (2010) is
10 guidance for registered providers on complying with the [Health and Social Care Act 2008](#)
11 [\(Regulated Activities\) Regulations 2010](#).

12 Outcome 8 of the Essential standards of quality and safety (2010) includes standards for
13 cleanliness and infection control which relate to regulation 12 of the Health and Social Care
14 Act 2008 (Regulated Activities) Regulations 2010, but does not provide guidance for
15 compliance with regulation 12. Guidance for compliance with regulation 12 is set out in the
16 [Health and Social Care Act 2008 Code of Practice on the prevention and control of infections](#)
17 (Department of Health 2010). Compliance with the code of practice is assessed by the CQC.

18 The code of practice states that 'procedures should be in place to ensure prudent prescribing
19 and antimicrobial stewardship. There should be an ongoing programme of audit, revision and
20 update. In healthcare this is usually monitored by the antimicrobial management team or
21 local prescribing advisors'.

22 **5.2 Review question**

23 What interventions, systems and processes are effective and cost effective in reducing
24 antimicrobial resistance without causing harm to patients?

25 The aim of this review question was to identify any evidence for any intervention, system or
26 process that demonstrates an effect in reducing the emergence of resistance at a patient or
27 community level.

28 **5.3 Evidence review**

29 **5.3.1 Clinical evidence**

30 A systematic literature search (see appendix C.1.2.1) identified 11,235 references. After
31 removing duplicates, the references were screened on their titles and abstracts and each
32 included study was identified as being relevant for inclusion for review. Two hundred and
33 forty-five references were obtained and reviewed against the inclusion and exclusion criteria
34 as described in the review protocol for medication review (appendix C.2).

35 Overall, 225 studies were excluded because they did not meet the eligibility criteria. A list of
36 excluded studies and reasons for their exclusion is given in appendices C5 and C6.

37 Twenty studies met the eligibility criteria and were included. Also, 5 relevant studies (RCTs)
38 were identified from the references included in a number of systematic reviews that met the
39 eligibility criteria. One additional RCT, Lesprit (2013), was identified for inclusion from a
40 systematic review recommended by the GDG [see appendix D1.1, table 26 for details]. The
41 GDG noted that all of the included studies related to clinical management interventions.

1 Of the 26 included studies, 24 were RCTs investigating the effect of interventions that used
2 emergence of resistance as an outcome (see appendix D). The RCTs were quality assessed
3 using the NICE methodology checklist for randomised controlled trials and the evidence
4 across the outcomes was appraised using GRADE.

5 Two systematic reviews of RCTs were also found to be relevant. The Cochrane review by
6 Davey et al. (2013) included interventions to improve antibiotic prescribing for hospital
7 inpatients (89 included studies). However, none of the included studies in the Cochrane
8 review met the inclusion criteria for the NICE review (predominantly interrupted time series
9 analyses and no RCTs included for resistance outcomes). As well as including non-RCT
10 evidence, the very low quality of the included studies that looked at resistance was an issue.

11 The Cochrane review found that interventions to change antibiotic prescribing were
12 associated with a decrease in *Clostridium difficile*-resistant gram-negative bacteria,
13 methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococcus
14 (VRE). However, the authors found only 6 interventions (29%) with reliable data on a change
15 in antibiotic prescribing. This was reported as a major confounder in the evidence base
16 because (the authors report) there are not enough data to estimate the likely impact of
17 change in prescribing on microbial outcomes.

18 The other systematic review (Falagas et al. 2007) examined the use of high versus low dose
19 quinolones for prophylaxis in surgery (12 included studies). Studies from this review were not
20 separately extracted. The systematic reviews were quality assessed using the NICE
21 methodology checklist for systematic reviews.

22 The 24 RCTs included were mainly carried out in adult populations (19 studies); 3 studies
23 looked at interventions in children; 1 study focused on hospital and healthcare staff; and 3
24 did not specify a population. Ten of the studies had interventions for prophylactic use of
25 antibiotics and 14 examined interventions in the treatment of infection. Three studies looked
26 at procedural or other interventions.

27 In most of the included studies, the emergence of resistance was a secondary rather than
28 primary outcome. It may be important to consider whether the studies were powered to
29 adequately detect differences in emergence of resistance, especially since in many cases
30 where a significant difference in antimicrobial resistance was noted, a test of small numbers
31 (for example, Fishers exact test) was used.

Table 5: Summary of included studies

Study	Population	Intervention(s)	Comparison	Key critical outcomes
Bouadma (2010) <i>France</i>	Adults with suspected bacterial infection admitted to, or who developed sepsis while in intensive care.	Study of treatment for sepsis. Procalcitonin (PCT) concentration to decide whether antibiotics should be commenced, and Serial serum PCT to help decide when to stop antibiotic therapy.	A single pre-study commencement reminder including recommendations for the duration of antimicrobial treatment for common infections derived from guidelines.	<ul style="list-style-type: none"> • Emergence of organisms resistant to antimicrobials • Clinical outcomes • Unintended consequences • Hospitalisation and health and social care utilisation
Brust (2011) <i>USA</i>	Adult methadone maintained patients who were HIV positive, on antiretroviral therapy, on a stable dose of methadone for 2 weeks before the baseline study visit.	Study of prophylaxis in community setting. Directly observed antiretroviral therapy.	Treatment as usual (self-administered therapy).	<ul style="list-style-type: none"> • Emergence of organisms resistant to antimicrobials • Clinical outcomes • Patient adherence
Capellier (2012) <i>France</i>	Adults mechanically ventilated for more than 24 hours and less than eight days, who had developed early-onset ventilator associated pneumonia.	Study of treatment for ventilator associated pneumonia. Immediate treatment with beta-lactams for 8 days combined with an aminoglycoside for the first 5 days.	Immediate treatment according to severity and any direct bacteriological results from BAL if available. Patients were treated with beta-lactams for 15 days combined with an aminoglycoside for the first 5 days.	<ul style="list-style-type: none"> • Emergence of organisms resistant to antimicrobials • Clinical outcomes • Unintended consequences • Hospitalisation and health and social care utilisation
Chardin (2009) <i>France</i>	Adults undergoing tooth extraction eligible for antibiotic prophylaxis.	Study of dental infection prophylaxis. Three days of amoxicillin (1g twice daily by mouth) and placebo for four days.	Seven days of amoxicillin (dose not described).	<ul style="list-style-type: none"> • Emergence of organisms resistant to antimicrobials • Clinical outcomes
Chastre (2003) <i>France</i>	Adults admitted to intensive care unit and mechanically ventilated for at least 48 hours with	Study of treatment for ventilator associated pneumonia. Treatment for 8 days with an aminoglycoside or a fluoroquinolone	Treatment for 14 days using the same protocol as per intervention.	<ul style="list-style-type: none"> • Emergence of organisms resistant to antimicrobials • Clinical outcomes

Study	Population	Intervention(s)	Comparison	Key critical outcomes
	suspected ventilator associated pneumonia.	and a broad spectrum beta-lactam.		<ul style="list-style-type: none"> • Unintended consequences • Hospitalisation and health and social care utilisation
Copenhagen study group of urinary tract infections in children (1991) <i>Denmark</i>	Children (girls) diagnosed with urinary tract infection (UTI)	A study of treatment of UTI. Short course of antibiotics compared with longer course of antibiotics.	Third arm used a short course of a different antibiotic.	<ul style="list-style-type: none"> • Emergence of organisms resistant to antimicrobials • Clinical outcomes • Unintended consequences
Curran (2008) <i>UK</i>	Not stated, no detail of the type of patient or ward settings used in the study is reported by the authors.	A study of 2 governance processes: Wards receiving statistical process chart feedback Wards receiving statistical process chart feedback and structured diagnostic tools	Wards receiving no new feedback of either type.	<ul style="list-style-type: none"> • Emergence of organisms resistant to antimicrobials
Davey (2013) <i>UK</i>	Health professionals who prescribe antibiotics to hospital in-patients receiving acute care but excluding interventions for long-term care facilities.	The 89 included studies largely covered the choice of antimicrobial (timing of first dose or route of administration, 80 out of 95 interventions). The remaining interventions addressed the exposure of patients to antibiotics (decision to treat or duration of treatment).	Not applicable	<ul style="list-style-type: none"> • Emergence of organisms resistant to antimicrobials
Falagas (2007) <i>Greece</i>	The 12 included studies comprised 2979 patients with various infections.	Study of prophylaxis in surgery. Studies were included if they treated documented infections with at least two treatment groups (one receiving a higher dose of quinolones than the other) and for at least one patient the causative organism persisted during or after treatment.	Lower dose of quinolone than the intervention arm.	<ul style="list-style-type: none"> • Emergence of organisms resistant to antimicrobials • Clinical outcomes • Unintended consequences
Goldman (2005) <i>USA</i>	Adults with HIV infection.	Study of prophylaxis in community setting.	Fluconazole administered only for oropharyngeal	<ul style="list-style-type: none"> • Emergence of organisms resistant to antimicrobials

Study	Population	Intervention(s)	Comparison	Key critical outcomes
		200mg of fluconazole orally 3 times weekly on a continuous basis.	candidiasis or oesophageal candidiasis episodes.	<ul style="list-style-type: none"> • Clinical outcomes
Hasselgren (1984) <i>Sweden</i>	Adults scheduled to undergo vascular reconstructive surgery of the lower limbs or undergoing acute femoral embolectomy or thrombectomy.	Study of prophylaxis in surgery. Two intervention arms and patients were randomly assigned to receive either: 1 day therapy with cefuroxime, or 3 days therapy with cefuroxime.	Placebo control group	<ul style="list-style-type: none"> • Emergence of organisms resistant to antimicrobials • Clinical outcomes • Unintended consequences
Hemsell (1985) <i>USA</i>	Women undergoing elective abdominal hysterectomy.	Study of prophylaxis in surgery. One single 2g dose of cefoxitin Two single 2g doses of cefoxitin Three single 2g doses of cefoxitin, all with placebo blinding.	Between intervention arms.	<ul style="list-style-type: none"> • Emergence of organisms resistant to antimicrobials • Clinical outcomes • Hospitalisation and health and social care utilisation
Hemsell (1984) <i>USA</i>	Premenopausal women scheduled for abdominal hysterectomy.	Study of prophylaxis in surgery. One 2g dose of cefoxitin and 2 placebo doses	Three 2 g doses of cefoxitin.	<ul style="list-style-type: none"> • Emergence of organisms resistant to antimicrobials • Clinical outcomes • Unintended consequences • Hospitalisation and health and social care utilisation
Heyland (2008) <i>Canada</i>	Critically ill adult patients mechanically ventilated for ≥ 96 hours who developed suspected pneumonia whilst intubated and ventilated.	Study of treatment for ventilator associated pneumonia. Initial un-blinded therapy with meropenem (1g every 8 hours) and ciprofloxacin (400mg every 12 hours).	Initial un-blinded therapy with meropenem (1 g every 8 hours) alone.	<ul style="list-style-type: none"> • Emergence of organisms resistant to antimicrobials • Clinical outcomes • Unintended consequences • Hospitalisation and health and social care utilisation
Ishibashi (2009) <i>Japan</i>	Adults undergoing elective surgery for colon cancer.	Study of prophylaxis in surgery. A single dose of IV antibiotics post operatively 1 hour post-surgery	Four additional doses of IV antibiotics for 2 consecutive days.	<ul style="list-style-type: none"> • Emergence of organisms resistant to antimicrobials • Clinical outcomes
Lesprit (2013) <i>France</i>	Adults in surgical and medical wards.	Post-antibiotic prescription review by an infectious diseases physician with	Usual care by ward physician only.	<ul style="list-style-type: none"> • Emergence of organisms resistant to antimicrobials

Study	Population	Intervention(s)	Comparison	Key critical outcomes
		a recommendation to the prescriber.		<ul style="list-style-type: none"> • Clinical outcomes • Hospitalisation and health and social care utilisation
Maru (2007) <i>USA</i>	Individuals using illegal drugs, who were also HIV-seropositive and in receipt of or eligible for highly active antiretroviral therapy.	A community based study for HIV treatment. Directly administered antiretroviral therapy.	Self-administered therapy.	<ul style="list-style-type: none"> • Emergence of organisms resistant to antimicrobials • Clinical outcomes
McCormick (2005) <i>USA</i>	Children aged 6 months to 12 years with diagnosed non-severe acute otitis media (AOM).	Study of treatment for AOM. The intervention was watchful waiting (symptomatic treatment only).	Immediate antimicrobial therapy	<ul style="list-style-type: none"> • Emergence of organisms resistant to antimicrobials • Clinical outcomes • Unintended consequences • Hospitalisation and health and social care utilisation • Patient reported outcomes (parental satisfaction)
Moltzahn (2012) <i>Switzerland</i>	Adults undergoing temporary JJ stenting due to urolithiasis.	Study of prophylaxis of urinary tract infection. Peri-interventional (stent placement) antibiotic prophylaxis (1.2g amoxicillin/clavulanic acid intravenously) at time of anaesthetic.	Continued low-dose antibiotics.	<ul style="list-style-type: none"> • Emergence of organisms resistant to antimicrobials • Clinical outcomes • Unintended consequences
Mountokalakis (1985) <i>Greece</i>	Newly hospitalised adults with recent stroke and indwelling urinary catheters for urinary incontinence.	Study of prophylaxis of urinary tract infection. 3g ampicillin intramuscularly (IM) divided into 3 equal doses 1 hour before, at the time and 6 hours post catheterisation. 1g ampicillin IM every 8 hours.	No antibiotic.	<ul style="list-style-type: none"> • Emergence of organisms resistant to antimicrobials • Clinical outcomes
Palmer (2008) <i>USA</i>	Critically ill adults requiring mechanical ventilation for >3 days	Study of treatment for ventilator associated tracheobronchitis.	Saline placebo aerosolised.	<ul style="list-style-type: none"> • Emergence of organisms resistant to antimicrobials

Study	Population	Intervention(s)	Comparison	Key critical outcomes
	and expected to survive at least 14 days.	Aerosolised antibiotic choice based upon gram stain of tracheal aspirate secretions for 14 days, unless extubated earlier.		<ul style="list-style-type: none"> Clinical outcomes
Palmer (2014) <i>USA</i>	Adults, who were intubated, mechanically ventilated and expected to survive for at least 14 days.	Study of treatment for respiratory infection in mechanically ventilated patients. Aerosolised antibiotic choice based upon gram stain of tracheal aspirate secretions for 14 days, unless extubated earlier.	Saline placebo aerosolised.	<ul style="list-style-type: none"> Emergence of organisms resistant to antimicrobials Clinical outcomes
Revankar (1998) <i>USA</i>	Adults with HIV	Study of prophylaxis in community setting. 200mg of fluconazole orally per day.	fluconazole (for episodic therapy) dose not defined	Emergence of organisms resistant to antimicrobials Clinical outcomes
Stahl (1984) <i>USA</i>	Girls (aged 2 to 17 years) with symptoms of lower urinary tract infection and two sequential urine culture positives for the same organism.	A study of single-dose treatment for uncomplicated urinary tract infection. A single-dose of amoxicillin (50mg/kg orally maximum 3g)	Conventional amoxicillin therapy (30mg/kg/day orally in three divided doses for 10 days, maximum per dose 250mg).	Emergence of organisms resistant to antimicrobials Clinical outcomes
van Zanten (2006) <i>Netherlands</i>	Consecutive hospitalised adult patients requiring antibiotics for acute infective exacerbation of chronic obstructive pulmonary disease.	A study of intermittent versus continuous IV antibiotic treatment for respiratory infection. 2g of cefotaxime intravenously over 24 hours plus a loading dose of 1g (over 30 minutes) for 7 days	1g of cefotaxime three times daily for 7 days	Emergence of organisms resistant to antimicrobials Clinical outcomes
van der Wall (1992) <i>Netherlands</i>	Adult hospital patients admitted for surgery (vaginal repair, hip replacement or colorectal surgery).	Study of prophylaxis in surgery Ciprofloxacin 250mg (plus placebo) once daily Ciprofloxacin 500mg twice daily	Placebo control	Emergence of organisms resistant to antimicrobials Clinical outcomes

Abbreviations: HIV = Human Immunodeficiency Virus; BAL = Bronchial alveolar lavage; AOM = Acute otitis media; JJ stent not an abbreviation (refers to the pigtail shaped and of the stent used to secure it

1 Where applicable, the reported outcomes from the RCTs were assessed using GRADE (see
2 appendix D.2.1 for full grade profiles).

3 There was some pooling of studies, although this was limited because the outcome
4 measures used differed and the follow-up periods reported varied among the studies.

5 Mean differences (MDs) were calculated for continuous outcomes, as well as the risk ratios
6 (RR) for dichotomous data. Where a meta-analysis was possible, a forest plot was presented
7 (see appendix D.2.1).

8 **5.3.2 Health economic evidence**

9 No health economic evidence was identified for this review question.

10 **5.4 Evidence statements**

11 **5.4.1 Clinical outcomes**

12 Evidence from 10 RCTs (4 of very low quality, 5 of low quality and 1 of moderate quality)
13 reported on antimicrobial resistance and other critical outcomes in prophylaxis studies:

- 14 • Continuous versus intermittent administration of antimicrobials was used in 2 RCTs; no
15 significant difference was found for emergence of resistance in pooled analysis. A lower
16 CD4 cell count^a was found for continuous therapy at follow-up in 1 study.
- 17 • Short versus longer courses of antimicrobials were used in 7 RCTs; only 1 study (in
18 abdominal surgery) found a significant reduction in the emergence of resistant isolates.
19 There were fewer cases of significant bacteriuria in the short-course cohort in 1 small
20 study of urinary tract infection.
- 21 • Low dose versus higher dose was used in 1 RCT; no significant difference was found for
22 emergence of resistance or other clinical outcomes.

23 Evidence from 14 RCTs and 1 systematic review (1 of very low quality, 8 of low quality and 6
24 of moderate quality) reported on antimicrobial resistance and other critical outcomes in
25 treatment studies:

- 26 • Continuous versus intermittent treatment was used in 1 RCT; no significant difference was
27 found for emergence of resistance or other clinical outcomes.
- 28 • Directly administered or observed therapy versus self-administered therapy was used in 2
29 RCTs; no significant difference was found for emergence of resistance. Directly
30 administered therapy demonstrated significantly greater virological success (mean
31 reduction in HIV-1 RNA level and increased CD4 cell count compared with self-
32 administered therapy in 1 study).
- 33 • Inhaled antibiotics versus inhaled saline placebo in addition to systemic therapy for
34 ventilator-associated respiratory infection was used in 2 studies; a pooled analysis of 2
35 small RCTs found a significant reduction in the emergence of resistance in the inhaled
36 antibiotic cohort. Inhaled antibiotics were significantly associated with lower white blood
37 cell count at 14 days (end of therapy), clinical pulmonary infection score, sputum volume
38 per 4 hours and an increased percentage of patients with organisms eradicated.

- 1 • Short versus longer courses of antibiotics were used in 4 studies; no significant difference
2 was found for emergence of resistance. Short courses were significantly associated with a
3 higher number of antibiotic-free days at follow-up in 1 study.
- 4 • High versus low doses of quinolones were used in 1 systematic review; no significant
5 difference was found for emergence of resistance. Conflicting evidence was presented for
6 bacterial eradication, clinical failure, bacteriological failure and adverse events.
- 7 • Procalcitonin (PCT) serum level was used in 1 RCT; no significant difference was found
8 for emergence of resistance. Use of PCT levels was significantly associated with a lower
9 number of days without antibiotics compared with usual care.
- 10 • Monotherapy versus combination therapy was used in 1 RCT; no significant difference
11 was found for emergence of resistance. Monotherapy was significantly associated with
12 greater adequacy of initial therapy.
- 13 • Watchful waiting versus immediate antimicrobial therapy was used in 1 RCT; no
14 significant difference was found for emergence of resistance. There was significantly more
15 treatment failure and more pain felt by those in the watchful waiting group.
- 16 • Statistical process charts versus usual care were used in 1 RCT; all cohorts within the
17 study saw a significant reduction in cases of newly acquired MRSA in the study period.
- 18 • Post-antibiotic prescription review was used in 1 RCT; no significant difference was found
19 for emergence of resistance. The intervention was significantly associated with more
20 stopped courses, shortened duration of therapy, greater de-escalation (dose reduction
21 and reduced combination therapy), shorter courses of broad (but not narrower or
22 intermediate) spectrum antibiotics, shorter courses of intravenous administration and less
23 need for antibiotics for relapse of infection.

24 Evidence from 5 RCTs reported on the clinical and microbiological outcomes of de-escalation
25 of antimicrobial therapy.

- 26 • De-escalation (a review of patients' clinical condition and microbiological sample results
27 and possible amendment of treatment) was used in 5 RCTs. The intervention was not
28 associated with increased mortality (5 of the 5 studies) or length of stay (in 4 of the 5
29 RCTs; 1 RCT had slightly increased length of intensive care stay for de-escalation of
30 antimicrobials in patients with severe sepsis).

31 **5.4.2 Economic evidence**

32 No health economic evidence for this review question was identified.

33 **5.5 Evidence to recommendations**

34

35

Table 6: Evidence to recommendations

Relative values of different outcomes	<p>The GDG discussed the different interventions and outcomes. GDG members noted that all of the included studies related to clinical management interventions. In the included studies, antimicrobials were used for prophylaxis (10 studies) and treatment (14 studies) of infection. The following interventions were used:</p> <ul style="list-style-type: none"> • short versus longer courses of antimicrobials (11 studies) • continuous versus intermittent antimicrobial administration (3 studies) • high-dose versus low-dose antimicrobial (2 studies) • directly observed therapy (2 studies) • inhaled antibiotics in addition to systemic therapy (2 studies) • procalcitonin serum levels (1 study) (see also section 6)
---------------------------------------	--

	<ul style="list-style-type: none"> • combination therapy (1 study) • watchful waiting (1 study) • statistical process charts (1 study) • post-prescription review (1 study). <p>The GDG recognised that most of the studies included adult patients in hospital settings. Few studies included children or were conducted in a primary care setting (for example, a GP practice).</p> <p>The GDG noted that for the outcome of emergence of antimicrobial resistance many of the studies found little evidence favouring the interventions. However, the GDG agreed that this was because of an absence of good quality trials, with sufficient numbers of people taking part, rather than evidence that the interventions themselves had no effect on resistance.</p> <p>The GDG agreed that in many of the studies there was little difference in clinical outcomes (for example, number of deaths and severe illness) between the intervention and control groups. However, the GDG noted that a few studies in which an intervention reduced the emergence of resistance had slightly poorer patient outcomes.</p> <p>The GDG agreed that there is limited evidence for making strong recommendations on the use of interventions to reduce the emergence of resistance. The GDG also recognised that in many of the studies the outcomes were reported over relatively short time periods and there is uncertainty about the longer term effects of the interventions.</p>
Quality of evidence	<p>The GDG was aware that most studies were of low or very low quality. The GDG also recognised that where evidence was of higher quality, the study setting (for example, intensive care setting) or study population (for example, patients with HIV infection) limited the applicability to broader populations.</p> <p>The GDG was aware that many of the studies used the emergence of resistance as a secondary outcome rather than a primary outcome. The GDG was also aware that, when designing studies, investigators typically base the number of people to include on differences in the primary outcome. The GDG agreed that in some studies not enough people had been included to determine whether the intervention had made a real difference to the emergence of resistance.</p> <p>The GDG discussed whether any conclusion should be drawn from a small number of the studies that were close to indicating (statistically) that an intervention reduced the emergence of resistance. The GDG discussed the difficulty in drawing any conclusions, particularly in deciding whether the studies indicated a real difference in the emergence of resistance or not.</p> <p>The GDG discussed and agreed that better quality evidence was needed on the effectiveness of interventions, systems and processes to reduce the emergence of resistance. Studies should be adequately powered to detect reductions in the emergence of resistance.</p>
Trade-off between benefits and harms	Considerations before prescribing an antimicrobial

The GDG discussed the effect that antimicrobial use can have on antimicrobial resistance. The GDG agreed that the relationship is complex but that reducing the frequency or altering the type of antimicrobial used (for example, narrower spectrum antibiotics) is likely to minimise the development of resistance.

The GDG discussed the benefits and harms of prescribing antimicrobial treatment for infection, including the impact such decisions have on antimicrobial resistance. The GDG discussed and agreed that before prescribing an antimicrobial (whether for prophylaxis or treatment), prescribers should consider the benefits and harms for the individual patient and the wider population harms associated with the possible development of antimicrobial resistance. This may be considered by using the principles of risk assessment. The GDG agreed that prescribers should only prescribe antimicrobials when there is a clear indication for doing so and should document the reason in the patient's record.

The GDG discussed individual patient factors, highlighted by the evidence and their expert experience, that need to be considered when prescribing an antimicrobial. The GDG agreed that the most important factors were the risk of the development of antimicrobial resistance, possible interactions with other medicines, a patient's other illnesses, drug allergy and the risk of healthcare-associated infections. The GDG concluded that when a decision to prescribe an antimicrobial has been made prescribers should take into account the benefits and harms for an individual patient associated with the particular antimicrobial, including:

- the risk of antimicrobial resistance
- possible interactions with other medicines
- the patient's other illnesses (for example, the need for dose adjustment in a patient with renal impairment)
- any drug allergies (these should be documented in the patient's record – see the NICE guideline on [Drug allergy](#))
- the risk of selection for organisms causing healthcare-associated infections (for example, *C. difficile*).

The GDG also discussed the need for patients and/or their family members or carers (as appropriate) to be involved in decisions about antimicrobials in line with the NICE guidelines on [Patient experience in adult NHS services](#) (CG138) and Medicines optimisation (publication expected March 2015). The GDG concluded that prescribers should take time to discuss with the patient and/or their family members or carers (as appropriate):

- their views on antimicrobials, taking into account their priorities or concerns for their current illness and whether they want or expect an antimicrobial
- the likely nature of the condition
- why prescribing an antimicrobial may not be the best option
- in self-limiting conditions consider alternative options to prescribing such as:
 - not prescribing
 - self-care with over-the-counter preparations
 - delayed prescribing (see the NICE guideline on [Respiratory tract infections](#))
 - non-pharmacological management – for example draining the site of infection
- the benefits and harms of immediate antimicrobial prescribing

- what they should do if their condition deteriorates (safety netting advice)
- offer written information in support of any advice given.

The GDG was aware that it is often difficult for a prescriber to decide whether to issue a prescription immediately to treat a possible bacterial infection or to delay treatment to see whether the infection resolves on its own (see section 6). The GDG discussed that when the infection is not severe it would be best practice to wait for microbiological sensitivity data before prescribing an antimicrobial. However, the GDG was aware that this may not always be feasible (for example, microbiological testing is used infrequently in primary care where over 80% of antimicrobial prescriptions are issued). In addition, the GDG was aware that in some instances microbiology results can be unintentionally misleading and can lead to possible over treatment.

The GDG discussed the possible value of point of care tests in determining whether an infection is bacterial or viral and their possible value in informing decisions about antimicrobial prescribing (see section 6).

The GDG concluded that prescribers should consider obtaining microbiological cultures before deciding whether to prescribe an antimicrobial for a non-severe infection, providing it is safe to withhold treatment until the results are available.

The GDG discussed the importance of selecting the most appropriate antimicrobial for the condition being treated. Guidelines to support appropriate antimicrobial use are important for achieving a consistent approach to managing infection. The GDG discussed the benefits of developing local guidelines collaboratively to cover primary and secondary care. The GDG agreed that the local antimicrobial formulary choice should be based on local patterns of antimicrobial resistance. The GDG agreed that prescribers should use local guidelines based on local patterns of resistance to prescribe antimicrobials (see section 8).

The GDG discussed antimicrobial prophylaxis in patients having surgery and agreed that as a set of general principles the [Start Smart, -Then Focus](#) guidance (Department of Health 2011) provides a useful set of criteria for prescribers.

The GDG discussed how reducing prescribing of broad spectrum antibiotics has led to short term reductions in the emergence of resistance. However, the GDG was aware that changes in patterns of resistance depend upon antimicrobial type, dose, frequency of administration and the way in which the individual antimicrobial works.

The GDG noted that the study by McCormick et al. (2005), which included children being treated for acute otitis media, found that watchful waiting reduced the emergence of resistance compared with immediate antimicrobial treatment but also led to possible poorer clinical outcomes. However, the GDG was aware that the outcomes were subjective and the outcome assessors (the children's parents) were not blinded to treatment allocation. The GDG was also aware of evidence from studies of delayed prescribing that showed no differences in clinical outcomes. The GDG noted that some of the antimicrobials used in these studies had a narrower spectrum of activity than others; unfortunately the results were not analysed to reflect the differences between the antimicrobials.

	<p>The GDG was aware that the NICE guideline on respiratory tract infections covers antibiotic prescribing for the same population and condition as covered by McCormick et al. (2005) – children with acute otitis media. Recommendations in the guideline set out when and when not to use ‘no antibiotic’ or ‘delayed antibiotic prescribing’. See also section 6.</p>
<p>Trade-off between benefits and harms for specific interventions</p>	<p>Short courses versus longer courses of antimicrobials</p> <p>The GDG noted that there was very limited evidence for the use of short course versus longer course antimicrobials as prophylaxis. The GDG was aware of NICE guidance on infection and surgical site infection and also the NICE quality standard on surgical site infection that provides advice and sets standards for antibiotic prophylaxis.</p> <p>The GDG discussed the evidence for short versus long courses of antimicrobial treatment and found insufficient evidence on the emergence of resistance. The GDG noted that the study by Chastre et al. (2003) found a lower emergence of antimicrobial resistance in mechanically ventilated patients receiving short versus long courses of antimicrobials for recurrence of pulmonary infection. However, when the results were pooled with those from another study (Capellier et al. 2003) no significant difference was found. The GDG noted that Capellier et al. (2003) found significantly more secondary infections in the short-course group.</p> <p>The GDG discussed the results of the studies of shorter versus longer courses of antimicrobials. The GDG agreed that the relationship between course duration and the emergence of resistance is likely to be complex, with potential for poorer clinical outcomes if the length of course is not sufficient to effectively treat the infection. The GDG agreed that more evidence was needed on course length in relation to antimicrobial resistance, but that in the meantime, duration should be the minimum necessary to effectively treat the infection.</p> <p>The GDG concluded that prescribers should follow local prescribing guidelines and consider prescribing the shortest effective course of antimicrobial treatment.</p> <p>The GDG agreed that it is not uncommon for hospital patients to stay on antimicrobial treatment for longer than intended. The GDG agreed that patients should remain on antimicrobials no longer than clinically necessary, and that systems and processes need to be in place to support the shortest clinically effective course. The GDG was aware that in some circumstances more doses of antimicrobial are dispensed than needed for the prescribed length of course because of the available pack size or limitations of some electronic prescribing systems. The GDG was concerned that patients would ‘finish the pack’ supplied rather than ‘finish the course prescribed’ and possibly suffer unnecessary side effects in the process.</p> <p>The GDG agreed therefore that health professionals should prescribe antimicrobials in accordance with local guidelines. The GDG also concluded that as a matter of patient safety organisations should aim to stock antimicrobials in pack sizes that correspond to local guidelines on course lengths (for example, consider pack sizes in urgent care settings or settings in which pre-packaged quantities are supplied).</p> <p>High versus low dose antimicrobials</p>

The GDG discussed the evidence for the use of high versus low dose antimicrobials for the prophylaxis and treatment of infection and agreed that there was an absence of evidence for the emergence of resistance. Evidence on clinical outcomes was conflicting for treatment of infection, but no difference was found for prophylaxis.

The GDG discussed the trade-offs of benefits and harms between using high and low doses of antimicrobials in relation to the emergence of antimicrobial resistance. The GDG was concerned that low doses might lead to poorer clinical outcomes and may result in incomplete treatment of an infection. This may mean that the patient needs another course of an antimicrobial. The GDG agreed that this could lead to an increase in antimicrobial resistance. The GDG agreed that there was not enough evidence to make recommendations for the antimicrobial dose for prophylaxis or treatment of specific conditions or in specific settings, but that antimicrobial prescribing should be based on clinical indication, be in line with local and national guidelines and take into account local patterns of resistance.

The GDG concluded that the most appropriate dose for each individual patient be determined in line with local antimicrobial prescribing guidelines and based on local patterns of resistance.

Continuous versus intermittent antimicrobials

The GDG discussed the evidence for continuous versus intermittent antimicrobials for prophylaxis and/or treatment of infection and agreed that there was an absence of evidence about antimicrobial resistance. The GDG noted that there was variation in the use of the terms continuous and intermittent therapy. In the 2 studies of prophylaxis, the intervention was regular (defined as continuous by the study authors) therapy to prevent infection compared with the intermittent treatment of infections in patients with HIV. In the single study looking at treatment of infection, a continuous infusion of antibiotic was compared with intermittent infusions of antibiotics for the treatment of chest infections in people with chronic obstructive pulmonary disease.

The GDG discussed whether any of the clinical findings from the prophylaxis studies could be applied to wider populations. The GDG agreed that because of the nature of the illness and the outcome measures used (patients with HIV infection and the CD4 cell count) the findings could not be applied to wider populations.

The GDG was aware that other patient groups may need continuous antiviral prophylaxis (for example, patients with organ transplants). The GDG was aware that long-term use of continuous prophylaxis in these groups can lead to antimicrobial resistance. However, the GDG agreed that the immediate clinical need in this situation outweighs the risk of the emergence of resistance.

The GDG concluded that prescribers should not issue repeat prescriptions for longer than 6 months without review. This includes repeat prescriptions for patients prescribed longer courses of antimicrobials for prophylaxis. The GDG acknowledged that a more frequent review may be needed dependent upon the patients' individual circumstances.

Directly observed therapy versus self-administered therapy

The GDG discussed the evidence from the 2 studies that compared directly observed therapy (patients taking their medicine in the presence of a healthcare worker) with self-administered therapy. Neither study found a difference in the emergence of resistance, but in 1 study clinical benefits were seen for directly observed therapy. However, the GDG agreed that because of the nature of the illness (HIV infection) and the condition-specific nature of the outcome measures (CD4 cell count and HIV-1 RNA level) the evidence could not be applied to wider populations. The GDG also agreed that there is a lack of justification for using this intervention in relation to antimicrobial resistance at present because there is not sufficient threat to warrant widespread directly observed therapy.

Studies in intensive care settings

The GDG discussed the evidence from studies of inhaled antibiotics in addition to systemic antibiotic therapy, studies of procalcitonin serum levels to guide antimicrobial therapy and studies of combination versus mono-antimicrobial therapy. The GDG agreed that the findings in critically ill patients in intensive care units could not be applied to wider populations at this time.

The GDG acknowledged that the studies of inhaled antibiotics in addition to systemic therapy did show some short-term benefit in reduced emergence of resistance, but GDG members were concerned that the follow-up period (14 days) was too short and that longer term trends in the emergence of resistance may not have been captured.

Statistical process charts versus usual care

The GDG noted that a single study examined the use of statistical process charts (a quality control process measuring the number of MRSA cases). The GDG discussed the study's findings and agreed that they appeared to be confounded by broader changes in infection control processes during the course of the study. This meant that all study arms showed a statistically significant reduction in MRSA cases at follow-up (including in the control arm). Because the intervention arms were not compared with each other (only themselves in a previous time period), the GDG concluded that they could not determine if there was a real effect in the intervention groups.

Narrow (limited) spectrum versus broad spectrum antimicrobials

The GDG agreed that using narrower (or limited) spectrum rather than broad spectrum antimicrobials was likely to reduce the emergence of resistance. However, the GDG agreed that there may be barriers to using narrow-spectrum antimicrobials. For example, a lack of point of care testing in primary care (see section 6.4.1), to establish the likely sensitivity of a microorganism, may mean that broader but still limited spectrum antimicrobials may be clinically preferable.

The GDG was aware that in secondary care broad spectrum antimicrobials are likely to be used initially because infections that require patients to be admitted to hospital are likely to be more severe. Broad spectrum antimicrobials are also used in patients who have additional risks (for example, those with weakened immune systems or additional health problems). However, the GDG agreed that in secondary care there is more scope for review of therapy and that antimicrobial therapy could be reviewed and possibly changed (also known as de-escalation) at between 48 and 72 hours depending on the patient's condition and the

microbiological sensitivity results. The GDG agreed that sample cultures should be obtained from hospital patients with suspected infection but without known diagnosis to allow an appropriate review.

The GDG was aware of the principles set out in the Department of Health's [Start Smart, -Then Focus](#) guidance for hospital care and found evidence to support some of these. However, the GDG was aware that 4 of the 5 RCTs on de-escalation were set in intensive care units; the remaining study also had a hospital setting. In addition all the studies were conducted in adult populations, and this limits the way in which the findings can be generalised.

The GDG discussed the evidence from a low quality RCT of de-escalation in intensive care for hospital-acquired pneumonia (Kim et al 2012). The GDG agreed that this study had limited applicability to the UK because the intervention used (carbapenem plus vancomycin) is not common first-line therapy for hospital-acquired pneumonia in the UK. The GDG was concerned that this study lacked allocation concealment, which may have meant those people who were more likely to have a resistant organism were placed in the intervention group rather than the control group. However, no significant between-group differences were noted for organisms isolated at baseline (gram positive or gram negative organisms). The GDG agreed that as a general principle the initial choice of broad spectrum antimicrobial may be important in reducing the emergence of resistance.

The GDG concluded that organisations should base formulary selection of empirical intravenous antimicrobials for patients who need treatment but do not have definitive diagnosis on national and local guidelines and local patterns of resistance. Prescribers should select an empirical intravenous antimicrobial from the agreed local formulary when a patient has a suspected infection needing intravenous treatment but has no confirmed diagnosis.

The GDG found no evidence from the RCTs that de-escalation at 48–72 hours increases patient mortality in either intensive care settings or hospital inpatient wards. The GDG also found that, with the exception of 1 low quality RCT of de-escalation in intensive care for severe sepsis (Leone et al 2014), there was no evidence that de-escalation at 48–72 hours increases the length of hospital or intensive care stay.

The GDG discussed the implications of the single RCT (Oosterheert et al. 2006) set in general hospital wards, rather than in an intensive care unit, which was the only study looking at switching clinically stable patients with community acquired pneumonia from intravenous antimicrobial therapy to oral therapy after 72 hours. The GDG was aware that community acquired pneumonia is a very common reason for hospital admission in the UK. The GDG agreed that early switching from intravenous to oral therapy reflects UK practice but acknowledged that there is a wide variation in this practice. The GDG discussed whether the move towards early switching from intravenous to oral therapy was evidence based. The GDG was aware that removing intravenous access, with the consequent reduction in the risk of MRSA bacteraemia, may have contributed to this change in practice. The GDG agreed that this study provides generalisable evidence that switching from intravenous to oral therapy following a review at 48–72 hours is safe.

The GDG concluded that prescribers should consider reviewing initial

	<p>intravenous antimicrobial prescriptions at 48–72 hours (in all care settings) to determine if the antimicrobial needs to be continued, and if so whether the intravenous antimicrobial can be switched to an oral antimicrobial. The GDG agreed that prescribers should document decisions from this review in the patients' record.</p>
<p>Trade-off between benefits and harms after prescribing an antimicrobial</p>	<p>Documenting decisions</p> <p>The GDG was aware of the need for effective communication of prescribing decisions, particularly in secondary care. The GDG discussed the need for adequate record keeping to allow for audits of prescribing. The GDG agreed that in line with the Public Health England 2013 publication, Antimicrobial prescribing and stewardship competencies, prescribers should document on the medicines chart or in the clinical record the clinical diagnosis or indication for treatment, the dose, frequency and duration of the antimicrobial course and a review date.</p> <p>The GDG concluded that prescribers should document in the patients' records:</p> <ul style="list-style-type: none"> • the reason for prescribing, or not prescribing, an antimicrobial • the plan of care, as discussed with the patient, their family member or carer (as appropriate). <p>Wherever possible, the GDG agreed, that to facilitate audits and monitoring of prescribing electronic methods of documenting decisions would be advantageous.</p>
<p>Implementation considerations</p>	<p>Antimicrobial resistance surveillance</p> <p>The WHO states that 'surveillance findings are needed to inform clinical therapy decisions, to guide policy recommendations, and to assess the impact of resistance containment interventions' and identifies that 'healthcare workers and public health authorities rely on the work and expertise of laboratory staff to determine:</p> <ul style="list-style-type: none"> • what organism is causing a patient infection • what antimicrobials would be effective treatment options'. <p>The GDG was aware of the need for improved access to resistance surveillance data in all settings, particularly in order to assess the impact of antimicrobial stewardship interventions. The GDG acknowledged that there may be difficulties in separating the effects of antimicrobial stewardship interventions from other activities particularly in secondary care settings (such as new hospital infection control processes, see also section 8.4.2). However the GDG identified that this was a particular concern for the out-of-hours, community and primary care settings. The GDG was aware that in secondary care, systems such as electronic prescribing and dispensing are yet to be linked to local data on resistance.</p> <p>The GDG agreed that, in line with WHO statement that 'surveillance findings are needed to inform clinical therapy decisions' better access for prescribers to local surveillance data is needed to guide appropriate choice of therapy.</p> <p>The GDG concluded that organisations should provide regular and timely feedback to individual prescribers in all care settings about:</p> <ul style="list-style-type: none"> • their antimicrobial prescribing (for example, by using professional regulatory numbers for prescribing as well as prescriber [cost centre] codes) • how their antimicrobial prescribing relates to local resistance patterns

	<ul style="list-style-type: none"> • those patients admitted to hospital with severe infection (for example, resistant infections), and consider discussing this with the prescriber if it is suspected that the infection and any complications could have been prevented. • patient safety incidents related to antimicrobials, including hospital admissions for rare or serious infections or associated complications (for example, mastoiditis, pyelonephritis, brain abscess, quinsy, empyema, meningitis or <i>C. difficile</i> infections) thought to be linked to a lack of or inappropriate antimicrobial prescribing. <p>The GDG was aware that only limited information exists on the value of information technology and decision support software in relation to the appropriateness of antimicrobial prescribing and the effects on antimicrobial resistance (see section 6.4.1.). However in their expert opinion the GDG concluded that there may be benefit from systems (such as clinical decision support systems) that prompt health professionals to consider treatment of symptoms as an alternative, and alternatives to immediate prescribing (for example, delayed prescribing), see section 6.4.1.</p> <p>The GDG agreed that commissioners have an important role to play in commissioning services with improved access to surveillance information and clinical decision support systems.</p> <p>The GDG also agreed that commissioners should consider how they can learn from services such as orthopaedic wound clinics, which currently make significant contributions to local surveillance and potentially more appropriate antimicrobial prescribing. These benefits could be transferred to GP wound clinics, which often deliver care closer to home and are preferred by many patients.</p> <p>The GDG was aware of resources for commissioners such as those produced by the TARGET initiative.</p>
Economic considerations	No relevant health economic evaluations were found that included outcomes of antimicrobial resistance.

1 5.6 Recommendations and research recommendations

2 5.6.1 Recommendations

3 See section 4.2 for a list of all recommendations and appendix F for a summary of the
4 evidence linking the recommendations.

5 5.6.2 Research recommendations

6 Uncertainties

7 This review question considered the interventions, systems and processes which aimed to
8 reduce the emergence of antimicrobial resistance while not adversely affecting patient
9 outcomes (in the treatment or prophylaxis of infection) when compared with usual care or
10 other intervention. The GDG agreed that the systematic review provided limited evidence for
11 this outcome and that a research recommendation would help to address the identified
12 uncertainty.

1 **Uncertainties may be related to:**

2 The clinical and cost effectiveness of interventions used to reduce the emergence of
3 antimicrobial resistance.

4 **Reason for uncertainty**

5 The emergence of antimicrobial resistance is a major threat to the health. The GDG agreed
6 that accurate and unbiased estimates of the effectiveness of interventions to reduce the
7 emergence of antimicrobial resistance should be obtained.

8 Randomised controlled trials have been undertaken on:

- 9 • short versus longer courses of antimicrobials and low dose versus higher dose
10 antimicrobials to reduce the emergence of antimicrobial resistance
11 • the effectiveness of directly administered (or observed therapy), continuous versus
12 intermittent therapy and inhaled antimicrobials in addition to systemic therapy on the
13 emergence of antimicrobial resistance.

14 However, these studies have considerable limitations such as sample size, lack of
15 applicability to UK populations, insufficient follow-up periods or conflicting results.

16 **Key uncertainties**

17 The key uncertainty is whether interventions reduce the emergence of antimicrobial
18 resistance and maintain patient outcomes from antimicrobial use compared to usual care, in
19 a UK setting. Including:

- 20 • short versus longer courses of antimicrobials
21 • lower dose versus higher doses of antimicrobials
22 • directly administered (or observed) therapy
23 • continuous versus intermittent therapy^b
24 • systemic antibiotic therapy with or without inhaled antibiotics

25 This uncertainty can be answered by doing more research into the area by conducting
26 studies that will deliver good quality evidence, such as a randomised controlled trial.

27 **Research recommendation**

- 28 **1. One or more randomised controlled trials should be undertaken to determine
29 whether short versus longer courses of antimicrobials, directly administered (or
30 observed) therapy, continuous versus intermittent therapy and inhaled
31 antimicrobials reduce the emergence of resistance and maintain patient outcomes
32 compared with usual care in the UK setting.**
33 **compared with usual care in the UK setting.**
34 **compared with usual care in the UK setting.**

35 The main outcomes should be patient-related clinical outcomes (for example, treatment
36 success and patient mortality) and unintended consequences (for example, secondary or
37 super infection). As well as the primary outcome of effect on emergence of resistance, the

1 GDG agreed that sample sizes should be calculated to also allow accurate assessment of
2 the emergence of antimicrobial resistant organisms.

3 Other outcomes of interest to the GDG were patient-reported outcomes (for example, quality
4 of life, satisfaction with care and medicines adherence), health and social care utilisation and
5 the cost-effectiveness of the interventions studied.

6 A follow-up period of at least 2–4 weeks after treatment for acute infection is recommended,
7 but longer term follow-up of 3–12 months would be needed for extended courses of
8 prophylaxis or treatment for longer term resistance outcomes.

9 Rationale

10 There is national surveillance evidence that shows that reduced prescribing or changes in
11 patterns of prescribing can slow the emergence of antimicrobial resistance. The evidence
12 considered by the GDG has shown that, at the level of the individual prescriber, studies of
13 antimicrobial stewardship interventions can reduce the amount or frequency of antimicrobial
14 prescribing. These interventions have not yet been linked to changes in the emergence of
15 antimicrobial resistance.

16 There is a need for evidence to consider the possible effect at the level of the individual
17 prescriber on the emergence of antimicrobial resistance. Measures that can appropriately
18 reduce antimicrobial prescribing and impact on the emergence of antimicrobial resistance in
19 clinical practice need to be considered.

20 PICO format:

Criterion	Explanation
Population	Those taking antimicrobials in any hospital or community setting in the UK.
Intervention	An intervention, system or process that occurs at the time of prescribing or during the course of the administration of an antimicrobial, with the intention of reducing the emergence of resistance of organisms in the patient undergoing prophylaxis or treatment including: <ul style="list-style-type: none">• shorter courses compared to longer courses of antimicrobials• higher compared to lower doses of antimicrobials• continuous compared to intermittent courses of antimicrobials• inhaled antimicrobials in addition to systemic antimicrobials.
Comparator(s)	Well defined routine care or usual care.
Outcome	Outcomes should consider: <ul style="list-style-type: none">• patient-related clinical outcomes (for example treatment success, mortality and secondary infection)• the emergence of organisms resistant to antimicrobials, measured through the development of microbial resistance from baseline to follow-up• patient-reported outcomes (for example quality of life, satisfaction, medicines adherence)• unintended consequences (adverse patient outcomes) for example patient death or secondary / super infection• hospitalisation and health and social care utilisation• how closely the individuals in the study have followed the prescribed course of antimicrobial treatment.
Study Design	Randomised controlled trial
Timeframe	A follow up period of at least 2 to 4 weeks after treatment for acute infection. A

	follow-up period of 3 to 12 months for extended courses of prophylaxis or treatment.
--	--

1

2

1 **6 Decision-making**

2 **6.1 Introduction**

3 Central to antimicrobial stewardship are the decisions made about antimicrobial use. These
4 decisions can ensure that antimicrobials are used when needed and not when there is no
5 clear clinical indication for their use. They may be influenced by many factors related to
6 individual patients and health professionals. This review question considers the processes
7 that may be effective in influencing decision-making and promoting antimicrobial
8 stewardship.

9 **6.2 Review question**

10 What interventions, systems and processes are effective and cost effective in changing
11 health and social care practitioners' decision-making to ensure appropriate antimicrobial
12 stewardship?

13 **6.3 Evidence review**

14 **6.3.1 Clinical evidence**

15 There were 2 searches undertaken for this review question (see appendix C.1.2.2). The
16 initial search included the interventions, systems and processes that may be effective in
17 changing the antimicrobial prescribing decisions of prescribers. This search identified 5160
18 references.

19 The second search was undertaken to specifically consider point-of-care tests and their
20 possible role in the decision to initiate antimicrobial therapy. Initial consideration of the
21 studies for potential inclusion in the evidence for this review question was discussed and
22 GDG members agreed that it had not included point of care tests and their possible role in
23 decision-making. The additional search to specifically search for RCTs of point of care tests
24 (procalcitonin and C-reactive protein) related to practitioner decision-making. This search
25 identified 5576 references.

26 After removing duplicates the references were screened on their titles and abstracts and
27 each included study was identified as being relevant for inclusion for review. Therefore a total
28 of 10736 titles and abstracts were screened against the inclusion and exclusion criteria as
29 described in the review protocol (appendix C.2). Two hundred and forty six full papers were
30 ordered and from these, 1 Cochrane review (Spurling 2013) and 11 RCTs (Butler 2012,
31 Camins, 2009, Christakis 2001, Dranitsaris 2001, Fine 2003, Gerber 2013, Gjelstad 2013,
32 Linder 2009, McGregor 2006, Seager 2006, Solomon 2001) met the inclusion criteria for this
33 review. In consideration of the broad scope of possible included interventions in this review
34 the reference lists in the systematic review and review papers that had been identified in the
35 search were also searched. This yielded 1 further RCT (Shojania, 1998) that met the
36 inclusion criteria. One further RCT (Lesprit, 2012) was identified by members of the GDG. In
37 total 13 RCTs and 1 Cochrane review were included.

38 In addition, for the point-of-care tests, 1 Cochrane review (published after the search had
39 been completed) and 1 RCT (Gonzales, 2011) for C-reactive protein point-of-care tests, and
40 1 Cochrane review (Schuetz, 2013) and 3 RCTs (Baer, 2013; Esposito, 2011; Manzour,
41 2010) for procalcitonin point-of-care tests met the inclusion criteria and were included.

Table 7: Summary of included studies

Study	Study type	Population	Intervention	Comparator	Relevant outcomes
Butler (2012) <i>UK</i>	RCT	General medical practices	Educational programme – online, face-to-face, clinical practice with reflection	Care as usual	<ul style="list-style-type: none"> • Antimicrobial use
Camins (2009) <i>USA</i>	RCT	Urban teaching hospital	Multidisciplinary antimicrobial utilization teams (infectious diseases physician and infectious disease pharmacist) – provided structured verbal feedback on antimicrobial use (choice defined by hospital criteria)	Standard care (indication-based guidelines for prescription)	<ul style="list-style-type: none"> • Appropriate antimicrobial prescription • Mortality • Length of stay
Christakis (2001) <i>USA</i>	RCT	Outpatient teaching clinic	Evidence based prompts – pop-up screens based on their selection of antibiotic, indication and duration	No evidence based prompts	<ul style="list-style-type: none"> • Duration of therapy
Dranitsaris (2001) <i>Canada</i>	RCT	Hospital sites	Cefotaxime prescriptions contrary to guidelines – physicians contacted by pharmacist for therapeutic modification (educational outreach for those who did not modify therapy)	Prescriptions reviewed, physicians not contacted	<ul style="list-style-type: none"> • Appropriate antimicrobial prescription
Fine (2003) <i>USA</i>	Cluster RCT	Hospital sites	Practice guideline and intervention, placement of a detail sheet into medical record, follow-up recommendation to attending physician, offer to arrange follow-up home nursing care	Practice guideline alone	<ul style="list-style-type: none"> • Duration of therapy • Length of stay
Gerber (2013) <i>USA</i>	Cluster RCT	Paediatric primary care practices	Clinical education with audit and feedback of antibiotic prescribing	Practices aware of the study, no education or prescribing feedback	<ul style="list-style-type: none"> • Antimicrobial use
Gjelstad (2013) <i>Norway</i>	Cluster RCT	Continuing medical education groups	Academic detailing, including reflection on individual prescribing rates and practices	Intervention targeting more appropriate drug treatment in those >70 years, used same procedures as for the antibiotic intervention	<ul style="list-style-type: none"> • Antimicrobial use
Lesprit (2012)	RCT	University hospital	Post-prescription review by infectious disease physician in addition to	Antimicrobial stewardship programme, no prescription review	<ul style="list-style-type: none"> • Duration of therapy

Study	Study type	Population	Intervention	Comparator	Relevant outcomes
<i>France</i>			antimicrobial stewardship programme		<ul style="list-style-type: none"> • Mortality • Length of stay
Linder (2009) <i>USA</i>	RCT	Primary care clinics	Acute Respiratory Infection (ARI) smart form – launched from notes page of electronic health record; provides decision support including antibiotic choice based on national recommendations	Usual care	<ul style="list-style-type: none"> • Antimicrobial use
McGregor (2006) <i>USA</i>	RCT	Tertiary care referral centre	Antimicrobial management team – infectious diseases physician and pharmacist	Standard care	<ul style="list-style-type: none"> • Mortality • Length of stay
Seager (2006) <i>UK</i>	RCT	General dental practitioners	Educational material (by post); guidelines, laminated page summary, patient information leaflets Educational material and academic detailer	No intervention	<ul style="list-style-type: none"> • Antimicrobial use • Appropriate antimicrobial prescription
Shojania (1998) <i>USA</i>	RCT	Tertiary care hospital	Computer based intervention, showing computerised guidelines for ordering	Usual screen computer	<ul style="list-style-type: none"> • Antimicrobial use • Duration of therapy
Solomon (2001) <i>USA</i>	RCT	Hospital site	Educational intervention using academic detailing approach; research assistant reviewed data on patients prescribed the included antibiotics if considered unnecessary prompted academic detailers	No educational intervention	<ul style="list-style-type: none"> • Appropriate antimicrobial prescription • Mortality • Length of stay
Spurling (2013)	Cochrane review	Patients of all ages with acute respiratory tract infections	Delayed antibiotic prescribing in acute respiratory tract infection	Immediate antibiotics prescribing No antibiotic use	<ul style="list-style-type: none"> • Antimicrobial use • Adverse effects

Table 8: Summary of included studies (point-of-care tests)

Study	Study type	Population	Intervention	Comparator	Relevant outcomes
Procalcitonin (PCT)					
Baer (2013) <i>Switzerland</i>	RCT	1month to 18years, lower respiratory tract infection	Treatment based on PCT categories, assay time <30mins, emergency department	Treatment based on physician assessment and clinical guidelines	• Antimicrobial use
Esposito (2011) <i>Italy</i>	RCT	1month to 14years, community-acquired pneumonia	PCT guided decision to treat	Treatment guided by guidelines	• Antimicrobial use
Manzour (2010) <i>Canada</i>	RCT	1month to 36months, fever without source	PCT measurement to assist with decision to treat	Decision to treat left to attending physician	• Antimicrobial use
Schuetz (2013)	Individual patient data meta- analysis Cochrane review	Adults, acute respiratory infection	Initiation or discontinuation of antibiotic therapy based on PCT cut-off ranges	Management based on usual care or guidelines, without PCT measurements	• Antimicrobial use • Mortality
C-reactive protein (CRP)					
Aabenhus (2014)	Cochrane review	Children and adults, acute respiratory infection	CRP guided decision to treat	Standard care	• Antimicrobial use
Gonzales (2011) <i>USA</i>	RCT	Adults, new cough, acute respiratory infection	CRP and management algorithm medical chart guided decision to treat	Management algorithm medical chart	• Antimicrobial use • Length of stay

1 6.3.2 Health economic evidence

2 A systematic literature search (appendix C.1.2.2) was undertaken to identify cost
3 effectiveness studies that evaluated systems, interventions and processes for changing
4 health and social care practitioners' decision-making to ensure appropriate antimicrobial
5 stewardship. This search identified 2523 records, of which 2501 were excluded based upon
6 their title and abstract. The full papers of 22 records were assessed and 19 were excluded at
7 this stage. The excluded studies and reason for their exclusion are given in appendix C.5.2.

8 The 3 studies meeting the inclusion criteria were quality assessed using the NICE quality
9 assessment checklists for cost effectiveness studies.

10 The study by Jensen et al. (1997) is a US study of the cost effectiveness of abbreviated
11 intravenous therapy. The study has minor limitations. It was deemed partly applicable as the
12 intervention was of relevance to the review question and the population included in the study
13 is a sub-group (hospitalised patients with diagnosed infection) of the population covered by
14 this guideline. No UK studies or studies better matching the NICE reference case were
15 identified. A US healthcare system perspective was taken. The study is based upon data
16 from 2 controlled trials.

17 The US study by McGregor et al. (2006) examined the costs and consequences of a hospital
18 antimicrobial stewardship team supported by computerised clinical decision support. The
19 study was deemed partially applicable to the guideline, despite major limitations. It consists
20 of a cost-consequences analysis rather than a cost effectiveness analysis as reported by the
21 authors. The US study by Scheetz et al. (2009) is a cost-utility analysis of antimicrobial
22 stewardship team supported by computerised clinical decision support and has only minor
23 limitations. This study was also deemed partially applicable as in both studies the
24 intervention was of relevance to the review question and the study population (hospitalised
25 patients with diagnosed infection) is a subgroup of this guidelines population. A US
26 healthcare system perspective was taken.

27 The GDG was aware that the 3 studies were from the US and that this therefore limited their
28 direct generalisability to the UK setting. However, as the studies limited their included costs
29 and benefits to those from a direct payer (hospital or insurer) perspective, the GDG agreed
30 that the findings of these studies may apply in part to UK settings. These are summarised in
31 tables 9 and 10. The evidence tables for the included studies are shown in appendix D.1.3
32 and the quality assessment tables in appendix D.2.2.

33 For the point-of-care tests no further economic evidence was identified that met the inclusion
34 criteria.

35

36

37

38

39

40

41

42

1

Table 9: Economic evidence profile – abbreviated IV antibacterial therapy

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effects	Cost effectiveness	
Jensen (1997) Cost effectiveness of abbreviating the duration of intravenous antibacterial therapy with oral fluoroquinolones	Minor limitations ^{1,2}	Partially applicable ^{3,4}	Controlled trial data from two trials informed a decision tree model.	At level 4 ⁵ the mean cost \pm SEM was: Intervention: \$4818 \pm \$269 Control: \$5028 \pm \$294 (p=0.141)	The probability of clinical success: Intervention: 0.76 Control: 0.72 (p=0.7). The probability of treatment failure: Intervention: 0.19 Control: 0.21 (p=0.7). The probability of failure due to lack of efficacy: Intervention: 0.08 Control: 0.20 (p=0.03), and due to adverse drug reaction 0.11 and 0.01, respectively (p=0.02). Adverse events ⁶	No incremental analysis was performed. The cost effectiveness ratios were \$6339 for each successful outcome in the switch therapy group versus \$6983 in the standard group.	One way sensitivity analysis was conducted on the probability of treatment success, the cost per day of hospitalisation and drug cost were varied. At level 4 substantial drug acquisition cost changes were required before standard IV therapy became more cost effective. The model was not sensitive to hospitalisation costs. The model was sensitive to changes in the probability of treatment success (if standard IV therapy was effectiveness was increased by 8% to 80% and switch therapy was decreased by 6% to 70%).

¹ A decision tree is used which models the outcomes of treatment for first infection, however a Markov model could have been used to model secondary or superinfections.

² Unit costs of resources are taken from Medicare fee schedule for 1995

³ The patient population (hospitalised patients with diagnosed infection) is a subgroup the guideline population, although not a UK population.

⁴ US health care system (payer perspective)

Study	Limitations	Applicability	Other	Incremental	Uncertainty
⁵ Level 1: drug acquisition cost only; Level 2: level 1 plus costs of laboratory drug monitoring, treatment of adverse events, secondary antibacterials and preparation and administration; Level 3: level 2 plus costs of physician care, diagnostic and therapeutic procedures and outpatient visits; Level 4: level 3 plus the base cost per hospital day (\$US270)					
⁶ Adverse events which were probably related to a study drug occurred in 50% of switch therapy patients and in 33% of standard IV therapy patients (p=0.02). Additionally 3 patients died but this did not alter the results of modelling, and are not further discussed.					

1

Table 10: Economic evidence profile – antimicrobial management team with computerised clinical decision support system

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effects	Cost effectiveness	
McGregor, JC (2006) Impact of a computerized clinical decision support system on reducing inappropriate antimicrobial use: a randomized controlled trial	Major limitations ^{1, 2, 3}	Partially applicable ^{4, 5}	Authors state that this is a cost effectiveness analysis (CEA). No summary measure of health benefit was included by the authors (costs and benefits were not combined). Therefore, the study was effectively a cost-consequences analysis.	During the 3-month study period, the University of Maryland Medical Center spent \$285,812 on antimicrobials in the intervention arm and \$370,006 in the control arm.	No significant difference in patient mortality for in-hospital mortality ⁶ or length of hospitalisation ⁷ between intervention and the control arms. Fewer patients in the intervention than the control arm experienced diarrhoea as a side effect of antimicrobial use as indicated by testing for <i>C. difficile</i> , though the difference was not statistically significant ⁸ . There were also no significant differences in the number of positive <i>C. difficile</i> tests between the intervention and control groups.	No incremental analysis was performed. The intervention arm was associated with savings of \$84,194 (22.8%) (\$37.64 per patient in the intervention arm).	No sensitivity analysis was performed.
Scheetz, MH (2009) Cost	Minor limitations ^{10, 11}	Partially applicable ^{4, 12}	Decision analytic model with data	Total cost (Base case) Intervention:	Total QALYs (Base case)¹³: Intervention: 8.01	\$4089 per QALY ^{14, 15}	One-way sensitivity analysis: Non ICU ¹⁶ ICERs that

Study	Limitations	Applicability	Other	Incremental		Uncertainty
effectiveness analysis of an antimicrobial stewardship team on bloodstream infections: a probabilistic analysis			identified by a systematic review of the literature (experimental and observational studies and one clinical guideline report)	\$40144 Standard treatment: \$39776	QALYs Comparator: 7.92 QALYs	ranged from \$2014 to \$22696 per QALY. For ICU patients the ICER ranged from \$3358 to \$3683 per QALY. Probabilistic sensitivity analyses: 95% CI for the incremental cost effectiveness ratio ranged from dominant (cheaper and more effective) to \$24,379 per QALY.

¹ No modelling is used by the paper which reports outcomes and antimicrobial costs from an RCT

² Morbidity, recurrence, secondary infection, superinfection, adverse events and pain are not considered as part of the analysis.

³ Only the acquisition cost of antimicrobials is considered

⁴ The patient population (hospitalised patients with diagnosed infection) is a subgroup the guideline population, although not a UK population.

⁵ US health care system (payer perspective)

⁶ p=0.55

⁷ p=0.38

⁸ 5.7% vs. 6.6% patients in intervention and control arms, respectively; p=0.21.

⁹ p=0.49

¹⁰ Estimates of resource use were obtained from literature search

¹¹ Estimates of unit cost were obtained from literature search

¹² US Institutional perspective

¹³ Please note that the utility weights associated with having bloodstream infections were based on authors' assumptions.

¹⁴ This is the base case ICER for AST compared with standard care

¹⁵ Probability cost-effective: Results from the probabilistic sensitivity analysis demonstrated there was more than 90% likelihood that an AST would be cost effective at a level of \$10000 per QALY.

Study	Limitations	Applicability	Other	Incremental	Uncertainty
¹⁶ Probability of receiving an active antibiotic on general floors (non-intensive care unit (ICU) care)					

1

1 **6.4 Evidence statements**

2 **6.4.1 Clinical evidence**

3 **Outcomes**

4 Antimicrobial use

5 There were 9 RCTs of very low quality, 1 RCT of low quality and 1 Cochrane review
6 (included papers, very low quality) that reported on antimicrobial use:

- 7 • Clinical education/academic detailing was used in 5 studies (4 in primary care, 1 in dental
8 practice). These studies found lower prescribing rates with the intervention groups
9 compared with the control groups.
- 10 • Computer-based decision support or guidelines was used in 2 studies; 1 study found
11 lower prescribing rates with the intervention (in secondary care), the second study (in
12 primary care) found no significant difference between the intervention and control group.
- 13 • Infectious disease physician review was used in 1 study (in secondary care); this study
14 found reduced broad-spectrum antibiotic use with the intervention compared with the
15 control group.
- 16 • Delayed prescribing for adult respiratory tract infections was used in a Cochrane review.
17 This review found a reduction in antibiotic use where delayed prescribing was used
18 compared with immediate prescribing.

19 Appropriate antimicrobial use/selection of antimicrobial

20 There were 4 RCTs (very low quality) that reported on antimicrobial use/selection of
21 antimicrobial:

- 22 • Clinical education/academic detailing was used in 2 studies; 1 study (in dental practice)
23 found a decrease in inappropriate prescribing with the intervention and the second study
24 (in secondary care) found no difference between the intervention and control groups.
- 25 • Clinical pharmacist review was used by 1 study (in secondary care); this study found no
26 difference between the intervention and control groups.
- 27 • Antimicrobial stewardship or management programmes/multidisciplinary team review was
28 used in 1 study (in secondary care), with an increase in appropriate antimicrobial use with
29 the intervention group compared with the control group.

30 Duration of therapy

31 There were 3 RCTs (very low quality) that reported on duration of antimicrobial therapy:

- 32 • Computer-based decision support or guidelines was used in 2 studies (in secondary care).
33 One study found a decrease in duration of therapy with the intervention group compared
34 with the control group; the second study found no difference between the intervention and
35 control groups.
- 36 • Review of guideline use was used in 1 study (in secondary care), with no difference in
37 duration of therapy between the intervention and control groups.

38 Mortality

39 There were 3 RCTs (very low quality) that reported on mortality:

- 1 • Antimicrobial stewardship or management programmes/multidisciplinary team review was
2 used in 2 studies (in secondary care); no differences in mortality were found between the
3 intervention and control groups.
 - 4 • Clinical education/academic detailing was used in 1 study (in secondary care); no
5 differences in mortality were found between the intervention and control groups.
- 6 Point-of-care tests
- 7 One individual patient data meta-analysis (low quality) in adults with acute respiratory
8 infection found decreased initiation of antibiotic therapy with those using procalcitonin-guided
9 cut-off ranges compared with those using standard care.
- 10 Three RCTs (very low quality) involving children, found no difference in antibiotic use
11 between those using procalcitonin-guided therapy and those using standard care.
- 12 One individual patient data meta-analysis, in adults with respiratory infections, found no
13 difference in mortality with those using procalcitonin-guided cut-off ranges to initiate antibiotic
14 therapy compared with those using standard care.
- 15 One meta-analysis of 4 RCTs (very low quality), in those with acute respiratory infection,
16 found decreased antibiotic prescribing with those using C-reactive protein-guided antibiotic
17 therapy compared with those using standard care. One RCT (very low quality), in adults with
18 acute cough, found no difference in antibiotic prescribing between those using C-reactive
19 protein-guided treatment along with a management algorithm compared with those using the
20 management algorithm alone.

21 **6.4.2 Economic evidence**

- 22 Partially applicable evidence with minor limitations built on RCT data suggests that
23 abbreviating the duration of intravenous antibacterial therapy with oral fluoroquinolones is
24 likely to be a cost-effective use of NHS resources.
- 25 No relevant evidence was identified on the cost effectiveness of other types of switch therapy
26 other than the fluoroquinolones modelled in the study.
- 27 Partially applicable evidence from 2 studies, 1 with minor limitations built on systematic
28 review data and 1 with major limitations built on RCT data, suggests that an antimicrobial
29 stewardship team with computerised clinical decision support is likely to be a cost-effective
30 use of NHS resources.

31 **6.5 Evidence to recommendations**

32 **Table 11: Evidence to recommendations**

Relative values of different outcomes	<p>The GDG discussed the substantial European and UK national focus on the need to consider antimicrobial resistance and the need for effective antimicrobial stewardship. GDG members agreed that to effectively approach this issue antimicrobial stewardship programmes need to be established at organisational level.</p> <p>The GDG noted that the outcomes reported in the available evidence were relevant and important. Nonetheless the GDG members noted that few studies considered any effect of the intervention over a substantial follow-up period. This lack of long-term follow-up means that it is not known whether interventions result in a sustained change in antimicrobial prescribing.</p>
---------------------------------------	--

	<p>The GDG discussed the value of outcomes related to the duration of therapy (or course length). GDG members considered that duration of therapy may be a less useful outcome because the ideal course length for many antimicrobials is uncertain. However, the GDG agreed that the process for reviewing the duration of therapy should be considered. That is, when an antimicrobial has been prescribed; the duration of this therapy should not be assumed but should be reviewed against the patient's clinical condition. The GDG acknowledged that this may not be routinely possible within primary care settings because the patient may be seen only once during a particular infectious episode.</p> <p>The GDG discussed the evidence in terms of the implications both for patient outcomes and costs relating to length of patient stay in hospital.</p> <p>The GDG considered that length of hospital stay and mortality outcomes are important when considering interventions that may affect decisions about prescribing. Any changes in these outcomes would provide an important indication of possible benefits or harms of changes in prescribing resulting from the interventions.</p>
Trade-off between benefits and harms	<p>The GDG agreed that the included interventions and outcomes were relevant to decision-making on antimicrobial prescribing. However, GDG members considered that the interventions in the included studies were disparate in nature. They agreed that this makes the evidence challenging to assimilate and therefore made it difficult to specify the elements of any interventions that could be recommended. Also, many of the included studies were based outside the UK and reported on the use of an intervention within a single or small number of primary or secondary care settings. Therefore any extrapolation of the outcomes of these studies to recommendations for UK practice could be difficult.</p> <p>The GDG agreed that, in general, the outcomes of the included studies showed that the interventions did affect decision-making and could reduce or alter decisions about antimicrobial prescribing. The GDG members discussed that while the individual interventions or programmes used in the included studies were often quite different there were similarities in the overall approaches used. Consideration of this and further GDG discussion enabled GDG members to agree that interventions that could be effective in antimicrobial stewardship were:</p> <ul style="list-style-type: none"> • clinical education/academic detailing • computer-based decision support/guidelines • antimicrobial stewardship/management programmes or multidisciplinary team prescribing review • clinical pharmacist review • educational outreach • delayed prescribing • point-of-care testing. <p>The GDG discussed the potential role of the audit cycle as a driver for changing decision-making. The GDG members agreed that although there was no evidence that solely considered audit, audit was an integral part of many of the interventions included. The GDG members noted that feedback to prescribers was integral to many of the interventions investigated. The GDG agreed that this was likely to be an important part of any intervention aimed at changing prescribers' decision-making. The GDG also noted that ongoing data collection was important to allow for continuous review of the outcomes of any interventions (or components of interventions). The GDG members agreed that</p>

these data would be useful for short-term feedback or audit and for reviewing any longer term impact.

The GDG noted that there is likely to be a need to reiterate or repeat interventions relating to antimicrobial stewardship to encourage sustained changes in prescribing. No studies were identified that had used such repeated interventions. The GDG discussed whether the initial intervention could be effective in providing evidence for the need for changes and the outcomes that could be achieved. GDG members agreed that regular updates could reinforce any changes made as a result of the initial intervention. They also considered that the provision of both local and national data on prescribing and antimicrobial resistance would help to update prescribers and could promote discussion that would assist with peer comparison among health professionals.

The GDG was aware that different healthcare teams support antimicrobial stewardship in different healthcare settings. That is, in secondary care there are often specified teams that review ward-based prescriptions soon after prescribing. In primary care, medicines management teams may review antimicrobial prescribing when prescribing data are available. The GDG agreed the need for the consistent provision of these healthcare teams across all healthcare settings for the appropriate implementation of antimicrobial stewardship interventions. The GDG reviewed the evidence that had been included relating to antimicrobial resistance, practitioner decision-making and barriers to antimicrobial stewardship. They noted that integral to any effectiveness in these programmes was reviewing prescribing and resistance data, feedback, education and the supporting of those making decisions that could impact on antimicrobial stewardship. Therefore they agreed that these would be integral to the work of antimicrobial stewardship teams. GDG members considered that the consistent provision of teams to support antimicrobial stewardship would also help prescribers to adhere to the appropriate local formularies and guidelines. Teams could also feedback to prescribers on their adherence.

The GDG discussed and agreed that it was important for healthcare services to be structured sufficiently to support those who review and may challenge antimicrobial prescribing. It was agreed that this support needs to effectively enable those who may be challenging or questioning established decision-making processes (for example, to allow health professionals to appropriately challenge the antimicrobial prescribing of their colleagues).

The GDG noted that any system has to be able to consider the need to review and change antimicrobial prescribing while also ensuring that prescribers can meet the clinical needs of an individual patient. Flexibility also needs to be available to prescribe outside of the guidelines when appropriate. However, GDG members emphasised that when clinical need justifies prescribing outside the guidance, the reason for doing so should be documented. The GDG considered that a recommendation for prescribers to document a patient's diagnosis before any antimicrobial prescribing would ensure that the reason for the prescribing can be seen. The GDG also discussed the importance of raising awareness of antimicrobial prescribing issues among all health and social care practitioners and across all healthcare and public health settings.

The GDG discussed the need for antimicrobial stewardship programmes to be appropriately designed for the healthcare setting in which they are to be used. GDG members agreed that although the principle components of an intervention may be similar, those working within primary and secondary care

have different requirements and these should be reflected in any intervention.

The GDG discussed the need to consider different approaches for reviewing the duration of therapy in primary and secondary care. The GDG noted that in secondary care the '[Start Smart, - Then Focus](#)' initiative has embedded within it the need to consider both the indication for therapy and the duration of therapy when prescribing. The difficulties with reviewing duration of therapy after a prescription has been issued in primary care were discussed by GDG members. The GDG considered whether prescribers should be required to provide a documented reason if a prescription is for a longer duration than is suggested in the summary of product characteristics (SPC) or appropriate recent guidance or local formulary. The GDG also considered the use of long-term antimicrobials in primary care and discussed, in relation to antimicrobial stewardship and resistance, the need for regular review of these prescriptions. GDG members noted that this review should be informed by any changes in the guidance for the underlying condition.

The GDG discussed the studies included from the Cochrane review that included delayed prescribing for those with respiratory tract infections. The GDG noted that these studies provided consistent evidence that delayed prescribing reduced antimicrobial prescribing and did not show increased adverse events or reduced patient satisfaction. GDG members noted the lack of evidence for delayed prescribing with any other conditions. They further noted that delayed prescribing could involve a variety of approaches, such as post-dating the prescription, re-contacting the clinic to request a prescription, allowing patients to collect the prescription from the clinic and supplying the prescription and asking the patient to wait. The GDG considered (in line with the NICE guideline on [respiratory tract infections – antibiotic prescribing](#)) that delayed prescribing could be recommended as part of antimicrobial stewardship. The GDG also agreed the need to discuss the reasons for using delayed prescribing with patients or carers, and the need for advice on re-consultation if symptoms change.

The GDG discussed the included evidence relating to the use of point-of-care tests as a guide to whether antimicrobial therapy should be started. GDG members agreed that for these tests to be useful in clinical practice, they would have to be easy to use, produce rapid results and be cost effective.

The GDG agreed that there was consistent evidence relating to the reduction in prescribing when procalcitonin tests were used in adults with respiratory tract infection. The GDG noted that the evidence showed a reduction in the use of antimicrobials with a C-reactive protein point-of-care test in adults with acute respiratory infections without increases in re-consultations or reduced patient satisfaction. GDG members discussed the need for point-of-care tests to be compared with current clinical assessment (both in primary care and in emergency departments) or the use of interventions such as delayed prescribing that reduce prescription rates without the additional possible time and cost resources of the point-of-care test. The GDG agreed that point-of-care tests may assist decisions about antimicrobial use, but that there is currently insufficient evidence (both clinical and economic) that they reduce inappropriate prescribing compared with other methods.

The GDG agreed that when clinical assessment indicates that an antimicrobial would be inappropriate, immediate prescribing should not be used and delayed prescribing should be considered. The GDG noted that the NICE guideline on [respiratory tract infections – antibiotic prescribing](#) had recommended a number of conditions in which antibiotics were not to be prescribed. GDG members

	<p>considered that the general principle of not prescribing antimicrobials for self-limiting conditions could be inferred from this guideline and their agreed experience. When the assessment is less clear, the GDG agreed that following recommendations in the NICE guideline on pneumonia would be appropriate. This recommends the use of C-reactive protein tests for patients presenting with lower respiratory tract infection in primary care if it is not clear after clinical assessment whether antimicrobials should be prescribed.</p> <p>The GDG considered the studies that reported on length of stay and mortality and noted that these were not powered for these outcomes. While acknowledging the limitations of the small amount of evidence, the GDG considered it important to note that these studies did not find any evidence of adverse effects relating to the interventions. The GDG agreed that length of hospital stay and mortality data should be included in research programmes related to antimicrobial stewardship. Furthermore, the GDG discussed the importance of capturing data on length of stay in relation to antimicrobial stewardship interventions. If these data were to show reductions in length of hospital stay with the intervention, this would provide clinical and economic impetus for implementation of the interventions.</p> <p>The GDG agreed that the potential benefits in relation to patient outcomes and antimicrobial resistance of changing prescribers' decision-making warrants resources being allocated in this area. This may require both local and wider considerations of the resources needed.</p> <p>When considering changing prescribers' decision-making, the GDG noted the benefits to using systems and processes that are already in place. The GDG discussed the importance of ensuring that other national agencies work together to support safe and effective antimicrobial stewardship – for example, working with the Care Quality Commission (CQC) and their inspections for essential standards.</p>
Economic considerations	<p>For the point-of-care tests, there were no economic studies identified that met the criteria in this review. The GDG reviewed the related economic evidence and discussion considered in the NICE guideline on pneumonia. This had considered that conclusions on the cost effectiveness of procalcitonin could be drawn on the basis of clinical evidence and unit costs alone. Given the cost components, C-reactive protein was considered to be cheaper than procalcitonin and more clinically useful. The GDG agreed that this conclusion was reasonable.</p>
Quality of evidence	<p>The GDG agreed that although the included studies provided evidence that broadly indicated that the interventions investigated had an effect on the chosen outcomes, the GRADE assessment indicated that these studies were of very low quality.</p>
Other considerations	<p>The GDG discussed the difficulties in obtaining timely and accurate prescribing data and trends. The GDG members agreed that it would be helpful if electronic prescribing was more widely used and the group considered if it could be mandatory for antimicrobial prescribing; however, they were mindful that in some care settings this may be more challenging to implement, may be costly because it may require a whole system change, and therefore may not be feasible.</p> <p>The GDG discussed the collection and availability of national and regional data on antimicrobial prescribing and resistance. The GDG members emphasised the importance of these data being routinely collected and widely accessible. The GDG discussed that in primary care prescribing data are not available until</p>

approximately 10 weeks after prescribing. The GDG was also aware that in primary care the indication for treatment is not linked to prescribing data and that the only way to review appropriate prescribing is through audit of patient clinical notes and prescribing data.

1 **6.6 Recommendations and research recommendations**

2 **6.6.1 Recommendations**

3 See section 4.2 for a list of all recommendations and appendix F for a summary of the
4 evidence linking the recommendations.

5 **6.6.2 Research recommendations**

6 **Uncertainties**

7 This review question considered the interventions, systems or processes and practitioner
8 decision-making relating to antimicrobial use and included a search and review of the use of
9 point-of-care tests at the point of deciding on whether to start an antimicrobial. The GDG
10 found the systematic review provided limited evidence for this and agreed that a research
11 recommendation would enable to address the identified uncertainty.

12 **Uncertainties may be related to:**

13 The clinical and cost effectiveness of using point-of-care tests in the decision-making by
14 prescribers considering whether or not to prescribe an antimicrobial.

15 **Reason for uncertainty**

16 The search identified a small number of studies relating to the use of C-reactive protein or
17 procalcitonin point-of-care tests compared to standard care/guidelines in those presenting
18 with respiratory tract infections. The clinical evidence reviewed indicated that the use of
19 these tests could reduce antimicrobial use without leading to an increase in re-consultations
20 or reduced patient satisfaction. There was no economic evidence identified that met the
21 inclusion criteria for the point-of-care tests review.

22 **Key uncertainties**

23 Point-of-care tests have been used to reduce prescribing of antimicrobials. There were no
24 studies identified in the review for this guideline that considered the effectiveness of point-of-
25 care tests when compared to other interventions that may reduce prescribing. Furthermore
26 these other interventions (such as the use of delayed prescribing) may be non-invasive and
27 may require less practitioner time and/or training. Any studies that aim to reduce
28 antimicrobial use would need to include outcomes relating to patient symptoms, adverse
29 effects and patient satisfaction.

30 Due to these uncertainties the GDG agreed a research recommendation. The GDG
31 suggested that randomised controlled trials would be an appropriate method to use for
32 further research that would compare the use of point-of-care tests to other methods of
33 reducing antimicrobial use.

34 **Research recommendation**

1 **2. Randomised controlled trials should be undertaken to determine whether use of**
 2 **point of care tests in decision-making is clinically and cost effective when**
 3 **prescribing antimicrobials in children and adults presenting with respiratory tract**
 4 **infections.**

5 The use of point-of-care tests could promote the judicious use of antimicrobials and provide
 6 some support for changing practice for both practitioners and patients where antimicrobial
 7 use is considered to be inappropriate. The GDG considered that for those patients
 8 presenting with respiratory tract infections, research into the clinical and cost effectiveness of
 9 point-of-care tests compared with other methods of reducing antimicrobial use is needed.

10 The main outcomes should be antimicrobial prescribing, alongside patient-based outcomes
 11 such as duration of symptoms and patient satisfaction. The GDG discussed the possible
 12 medicalisation of those presenting with respiratory tract infections and considered that any
 13 changes in patient requests for point-of-care tests or in patient flow should also be identified.

14 **Rationale**

15 The need for the judicious use of antimicrobials alongside the concern about increasing
 16 resistance underpins antimicrobial stewardship.

17 Research in this area would enable stronger recommendations to be made in this area that
 18 could substantially contribute to reducing antimicrobial use and antimicrobial resistance.

19 Uncertainty in this area may be answered by doing more research into the area by
 20 conducting a study that is sufficiently powered and will deliver good quality evidence,
 21 randomised controlled trials.

22 PICO format:

Criterion	Explanation
Population	Those with respiratory tract infections
Intervention	Point-of-care tests used immediately prior to (<60 minutes) or during consultation
Comparator(s)	Use of delayed prescribing Other methods of reducing antimicrobial use
Outcome	Outcomes to be included should consider: <ul style="list-style-type: none"> • antimicrobial use • adverse events • duration and severity of symptoms • cost effectiveness • patient satisfaction • changes in patient requests for point-of-care tests or any impact on patient flow through primary care. <p>For results to be valid and reliable, outcomes should ideally be measured using validated tools, and where this is not possible the method of outcome measure should be detailed in the study.</p>
Study Design	Randomised controlled trial
Timeframe	3 months

1 7 Barriers to decision-making

2 7.1 Introduction

3 The goals of antimicrobial stewardship include using antimicrobial therapy appropriately and
4 minimising the development of antimicrobial resistance. To achieve these aims there may
5 need to be changes in practice and in decision-making by practitioners.

6 The aim of this review question was to identify any evidence for interventions, systems or
7 processes that are effective and cost effective in overcoming the barriers to decision-making
8 by health and social care practitioners when ensuring appropriate antimicrobial stewardship.

9 7.2 Review question

10 What interventions, systems and processes are effective and cost effective in overcoming
11 the barriers to decision-making by health and social care practitioners when ensuring
12 appropriate antimicrobial stewardship?

13 7.3 Evidence review

14 7.3.1 Clinical evidence

15 A systematic literature search was conducted (see appendix C.1.2.3) which identified 5218
16 references. After removing duplicates the references were screened on their titles and
17 abstracts and each included study was identified as being relevant for inclusion for review.
18 One hundred and thirty-five references were obtained and reviewed against the inclusion and
19 exclusion criteria as described in the review protocol (see appendix C.2.3).

20 Overall, 123 studies were excluded because they did not meet the eligibility criteria. A list of
21 excluded studies and reasons for their exclusion is provided in appendix C.5.3.

22 The search did not identify studies that directly considered interventions, systems and
23 processes that might be effective or cost effective in overcoming the barriers to decision-
24 making by health and social care practitioner's when ensuring appropriate antimicrobial
25 stewardship. However, 12 studies investigated what barriers exist for decision-making in
26 relation to antimicrobial stewardship by health and social care practitioners. These studies
27 therefore met the eligibility criteria and were included. In addition, 6 relevant systematic
28 reviews were identified. The references included in these systematic reviews were also
29 screened on their titles and abstracts to identify any further studies that met the eligibility
30 criteria. Four additional studies were included.

31 Of the 16 studies included, 9 were qualitative (semi-structured interviews or focus groups)
32 and the remaining 7 were cross-sectional surveys (see appendix D.1.3). The qualitative
33 studies were assessed using NICE's methodology checklist for qualitative studies.
34 [Developing NICE guidelines: the manual](#) (2014) does not provide a checklist for cross-
35 sectional surveys; therefore a checklist originally published in the British Medical Journal was
36 used for the quality assessment of these studies (see appendix H).

37 Available data were extracted into evidence tables (see appendix D.1.4) and are summarised
38 in table 12 below:

Table 12: Summary of included studies

Study	Population	Study Type	Key Results
Abbo (2013) <i>USA</i>	Clinicians from 82 acute care facilities	Cross-sectional study	The following barriers to implementation were identified: <ul style="list-style-type: none"> • Lack of time • Personnel shortages • Inadequate funding
Bannan (2009) <i>Australia</i>	256 clinicians from the Concord hospital	Cross-sectional study	Key findings identified were: <ul style="list-style-type: none"> • 10% (95% CI: 6-16%) believed the antimicrobial restriction policy (ARP) did not value their intuition and experience • 33% (95% CI: 26-41%) believed the ARP policy was time-consuming and detracted from other clinical duties • 19% (95% CI: 13-25%) felt that the ARP policy was an infringement on their autonomy
Broom (2014) <i>Australia</i>	30 doctors who prescribe antibiotics at a hospital	Qualitative: Semi-structured interviews	Barriers identified included: <ul style="list-style-type: none"> • Antibiotic resistance was considered to be a lower priority compared to other day-to-day clinical priorities. • Patient outcomes were more of a concern than inappropriate antibiotic use. • Emotional and relational pressure to prescribe antibiotics. • Doctors prescribing activities appeared to be governed by micro-social peer networks and hierarchies.
Charani (2013) <i>England</i>	39 health professionals from 4 hospitals	Qualitative: Semi-structured interviews	The following barriers were identified: <ul style="list-style-type: none"> • Senior doctors rely on their own professional judgement when prescribing. • Doctors are uncomfortable challenging their colleagues practice. • Doctors use anecdotal experience to justify their clinical decisions for individual patients. • Local prescribing practices are driven by hierarchies.
Cortoo (2008) <i>Belgium</i>	22 participants from a tertiary care teaching hospital	Qualitative: Focus groups	Two key barriers were identified: <ul style="list-style-type: none"> • Prescribing practices of juniors is strongly influenced by supervisors • Pressure of work limited time to consult guidelines.
De Souza (2006) <i>Ireland</i>	22 participants from a 500 bed university teaching	Qualitative: Semi-structured interviews	From the analysis 3 key findings are relevant: <ul style="list-style-type: none"> • Senior colleagues have the most significant influence on prescribing practices

Study	Population	Study Type	Key Results
	hospital		<ul style="list-style-type: none"> • Individual teams had patterns of prescribing and standard ways of doing things. • More experienced doctors use their professional judgement and tacit knowledge when prescribing.
Doron (2013) USA	406 hospital pharmacists	Cross-sectional	Barriers to implementation included: <ul style="list-style-type: none"> • Staffing constraints. • Insufficient staff buy-in. • Competing priorities.
Hart (2006) USA	21 primary care clinicians	Qualitative: Semi-structured interviews	A key finding was: <ul style="list-style-type: none"> • Prescribing decisions were based on what the clinician believed was best for the patient.
Heritage (2010) USA	38 paediatricians	A nested cross-sectional study	Two key findings were: <ul style="list-style-type: none"> • Reporting of abnormal physical examination findings during an examination may raise parental expectation for an antibiotic. • A physician's perception that a parent expects an antibiotic may influence prescribing behaviour.
Hersh (2009) USA	147 paediatric infectious disease consultants	Cross-sectional study	The major barrier identified: <ul style="list-style-type: none"> • Lack of resources (including funding, time, and personnel). • Respondents perceived antibiotic resistance as a more significant problem nationally than at their local hospital.
Johannsson (2011) USA	522 Infectious diseases physicians	Cross-sectional study	Major barriers identified (ranked in order) were: <ul style="list-style-type: none"> • Lack of funding and lack of personnel. • Other higher-priority clinical initiatives. • Administration not aware of value of antimicrobial stewardship program (ASP). • Opposition from other prescribers. • Lack of information technology support and/or inability to get data. • Other speciality's antagonised by ASP. Multiple infectious disease groups within the facility. <p>The authors concluded that the lack of funding remains a key barrier for ASPs, and administrators need additional cost savings data in order to support ASPs.</p>
Kumar (2003)	40 GPs	Qualitative: semi	Decision making:

Study	Population	Study Type	Key Results
<i>England</i>		structured interviews	The presence of adverse social factors lowered general practitioners' threshold for prescribing antibiotics for sore throat: <ul style="list-style-type: none"> • Clinical experience, length of service, and research evidence • Antimicrobial resistance • Maintaining patient/doctor relationship
Schouten (2007) <i>Netherlands</i>	18 care providers	Qualitative: Semi-structured interviews	The authors suggest interventions to overcome guideline barriers: <ul style="list-style-type: none"> • Improving physician's view/attitudes towards a guideline (rather than improving physician's knowledge). • Suggests involving local specialists to develop local guidelines based on evidence
Simpson (2007) <i>Wales</i>	40 GPs	Qualitative: Semi-structured interviews	Agreed AMS is a problem but they infrequently encountered its consequences [microbial resistance] locally Suggested <ul style="list-style-type: none"> • More information about resistance patterns locally • Enhanced practitioner training
Teo (2013) <i>Australia</i>	5 antimicrobial stewardship committee members (policymakers) and 15 prescribers	Qualitative: Semi-structured interviews	Barriers to compliance with the antibiotic prescribing policy: <ul style="list-style-type: none"> • Lack of knowledge. • Inapplicability of the antibiotic prescribing policy. • Prescriber autonomy and personal experience. • Organisational hierarchies. Overcoming barriers: <ul style="list-style-type: none"> • Involving prescribers in policy development. • Giving feedback about their prescribing. • Improving existing collaboration and decision support platforms.
Wigton (2008) <i>USA</i>	101 community practitioners and 8 faculty members	Qualitative	Practitioners prescribed antibiotics in 44.5% of cases, over twice the percentage treated by the panel using the Centers for Disease Control and Prevention (CDC) guidelines (20%). <ul style="list-style-type: none"> • Practitioners gave little or no weight to patient factors such as whether the patients wanted antibiotics. • Practitioners were most strongly influenced by duration of illness. The effect of duration was strongest when accompanied by fever or productive cough.

Study	Population	Study Type	Key Results
			<p>The authors suggest that these situations would be important areas for practitioner education.</p>
Wood (2007) <i>Wales</i>	40 GPs	Qualitative	<p>The study looked at GP surgeries with differing levels of prescribing broad-spectrum antibiotics (fluoroquinolone).</p> <ul style="list-style-type: none"> • GPs from high prescribing practices were more likely to prioritise patients' immediate needs. • GPs from average prescribing practices were more likely to consider longer term issues. • GPs from both high and average prescribing practices justified their antibiotic choices on the basis of a desire to do their best for their patients and society. <p>Prescribing was justified on the basis of social responsibility. Strategies to change broad-spectrum antibiotic prescribing will need to take into account clinicians' perceptions of social responsibility.</p>

1 7.3.2 Analysis of the included studies

2 Evidence was reviewed to identify barriers to decision-making by health and social care
3 practitioners when ensuring appropriate antimicrobial stewardship. From the included
4 studies, the barriers were grouped into 4 key areas:

- 5 • Clinical priorities
 - 6 ○ data
 - 7 ○ resistance patterns
 - 8 ○ prescribing patterns
 - 9 ○ feedback to prescribers
 - 10 ○ competing priorities
- 11 • Decision-making
 - 12 ○ knowledge
 - 13 ○ judgement
 - 14 ○ patient expectations
 - 15 ○ values
- 16 • Hierarchies or social structures
 - 17 ○ knowledge and judgement
 - 18 ○ willingness to challenge practice
- 19 • Resources
 - 20 ○ time
 - 21 ○ staffing
 - 22 ○ funding.

23 Due to the methods used in the included studies (cross-sectional and qualitative) the use of
24 the GRADE was not considered appropriate. The NICE checklist for qualitative studies was
25 used. A checklist originally published in the [British Medical Journal](#) was used to aid in the
26 quality assessment of the cross-sectional surveys. The search results did not identify studies
27 directly considering interventions, systems or processes to overcome barriers to decision-
28 making by health and social care practitioners when ensuring appropriate antimicrobial
29 stewardship. Evidence to demonstrate their effectiveness or cost effectiveness was also not
30 found. Studies included in the analysis identified barriers to appropriate antimicrobial
31 stewardship and some suggested interventions, systems or processes that may be effective
32 in overcoming these barriers. Therefore, 2 key themes matrices were used to present the key
33 themes from the included studies. One (see table 13) summarises the barriers to decision-
34 making and the other (see table 14) summarises key themes that were identified as potential
35 considerations for overcoming the identified barriers.

36

1
2

Table 13: Key themes matrix - barriers to decision making by health and social care practitioners when ensuring appropriate antimicrobial stewardship

Study	Clinical priorities	Decision making	Hierarchies/social structures	Resources
Abbo (2013)				Lack of time. Personnel shortages. Inadequate funding.
Bannan (2009)		10% (95% CI: 6-16%) believed the antimicrobial restriction policy did not value their intuition and experience. 19% (95% CI: 13-25%) felt that the ARP policy was an infringement on their autonomy.		Time consuming and detracted from other clinical duties.
Broom (2014)	Relative to other day-to-day clinical considerations, antibiotic resistance was of limited concern... Overtreatment...was viewed as more favourable than the potential for adverse immediate patient outcomes.	Emotional and relational pressures to “do everything possible” for a patient/family.	Doctors’ prescribing practices appeared to be governed by micro-social peer networks and hierarchies.	
Charani (2013)		Senior doctors rely on their own professional judgement and the need to freely choose what they judge to be the most appropriate... There is a clear shared view of “non-inference” when it comes to doctors judging or intervening in the prescribing behaviour of their colleagues. Doctors...frequently consider	The practice of prescribing is primarily performed by junior doctors, but it is the seniors who decide what needs to be prescribed.	

Study	Clinical priorities	Decision making	Hierarchies/social structures	Resources
		their patients to be “outside” the boundaries of local evidence-based policies.		
Cortoos (2008)			Supervisors practice strongly determined the subsequent prescribing behaviour of residents.	Pressure of work as a cause of not being able to consult guidelines.
De Souza (2006)		Decisions made by senior doctors tended to emphasise their individual assessment of the patient and application of the individual tacit knowledge base.	The most significant influence on prescribing practices was the opinion of more senior colleagues in the team. Individual teams had patterns of prescribing and standard ways of doing things.	
Doron (2013)				Staffing constraints
Hart (2006)	Ultimately, each clinician made a decision based on what he or she believed was best for the patient.			
Heritage (2010)		A physician’s perception that a parent expects an antibiotic may influence prescribing behaviour.		
Hersh (2009)	Respondents perceived antibiotic resistance as a national rather than local issue.			Lack of resources
Johannsson (2011)	Other higher priority clinical initiatives.		Other specialities were antagonised by antimicrobial stewardship programmes.	Lack of funding and personnel. Lack of information technology/inability to get data.

Study	Clinical priorities	Decision making	Hierarchies/social structures	Resources
Simpson (2007)	Many said they infrequently encountered its [microbial resistance] in their everyday practice and some questioned the evidence linking their prescribing decisions to resistance and poorer outcomes for their patients.			
Teo (2013)		Antimicrobial stewardship committee members attributed non-compliance to the policy to prescriber autonomy and personal experience.		
Wigton (2008)	Practitioners were most strongly influenced by duration of illness.	Practitioners gave little or no weight to patient factors such as whether the patients wanted antibiotics.		
Wood (2007)	GPs from high prescribing practices were more likely to prioritise patients' immediate needs.			

1
2
3

1

Table 14: Key themes matrix - interventions, systems or processes that may overcome identified barriers to decision making

Study	Communication	Education	Policy developments	Additional information
De Souza (2006)		Participants felt that undergraduates are not sufficiently trained to make autonomous antimicrobial prescribing decisions.		
Hart (2008)		By educating patients about the data informing their decision to not prescribe antibiotics, clinicians offered [said] they could often increase perceived patient satisfaction and successfully refrain from prescribing antibiotics.		
Heritage (2010)	With viral illnesses, problematic online comments are associated with more paediatrician-parent conflict over non antibiotic treatment recommendations. This may increase inappropriate prescribing. Physicians should consider avoiding the use of problematic online commentary.			
Johannsson (2011)				The authors concluded that the lack of funding remains a key barrier for ASPs, and administrators need additional cost savings data in order to support ASPs.
Simpson (2007)		Many of the GPs said they infrequently encountered its consequences in their everyday		More information from their microbiological colleagues about resistance patterns locally

Study	Communication	Education	Policy developments	Additional information
		<p>practice and some questioned the evidence linking their prescribing decisions to resistance and poorer outcomes for their patients.</p> <p>Undergraduate and graduate education about antimicrobial prescribing and resistance should be enhanced</p>		
Teo (2013)	Giving prescribers feedback about their prescribing may improve judicious antibiotic use		Involving prescribers in policy development may improve judicious antibiotic use.	Improving existing collaboration and decision support platforms may further improve judicious antibiotic use.
Wigton (2008)		<p>Based on hypothetical cases of acute respiratory tract infection, community practitioners prescribed antibiotics at twice the rate of a faculty following CDC practice guidelines.</p> <p>Practitioners were most strongly influenced by duration of illness. The effect of duration was strongest when accompanied by fever or productive cough, suggesting that these situations would be important areas for practitioner education.</p>		

1 7.4 Health economic evidence

2 No health economic evidence was identified for this review question.

3 7.5 Evidence statements

4 7.5.1 Clinical evidence

5 Five cross-sectional studies and 1 qualitative study identified resources as a barrier to
6 implementation of antimicrobial stewardship activities. Resources included:

- 7 • lack of time
- 8 • insufficient of funding
- 9 • inadequate staffing.

10 In relation to hierarchies and social structures, 4 qualitative studies and 1 cross-sectional
11 study revealed the following key barriers:

- 12 • doctors prescribing practices are driven by micro-social structure
- 13 • senior doctors have a strong influence over the prescribing practices of junior colleagues.

14 In relation to clinical priorities, 4 qualitative and 3 cross-sectional studies identified clinical
15 priorities as a barrier to antimicrobial stewardship activities. These were:

- 16 • Immediate patient outcomes were more of a concern than antimicrobial resistance.
- 17 • Antimicrobial resistance was viewed as a national issue rather than a local problem and
18 was infrequently encountered.

19 In relation to decision-making, 5 qualitative and 2 cross-sectional studies suggested that:

- 20 • Senior doctors rely on their own professional judgement and tacit knowledge base.
- 21 • Non-compliance with antimicrobial policy was attributed to prescriber autonomy.
- 22 • A physician's perception of patient's expectations on antibiotics may influence prescribing
23 behaviour.
- 24 • There is a clear shared view of 'non-interference' when it comes to doctors judging or
25 intervening in the prescribing behaviours of their colleagues.

26 7.6 Evidence to recommendations

27 **Table 15: Evidence to recommendations**

Relative values of the different barriers identified	<p>The GDG was aware of the barriers identified in the included studies to decision-making by health and social care practitioners in relation to antimicrobial stewardship. Some of the studies suggested interventions, systems and processes to overcome the barriers identified, but none of them assessed the outcomes of these. No RCT evidence was identified to answer this review question; the evidence identified was from qualitative and cross-sectional studies.</p> <p>Decision-making when prescribing an antimicrobial</p> <p>The GDG discussed the evidence that health professionals view overtreatment as preferable to risking adverse patient outcomes and agreed that this happens in practice. The GDG further discussed situations in which health professionals prescribed antimicrobials 'just in case'. The GDG</p>
--	--

agreed that prescribers should be empowered to refuse to prescribe antimicrobials when this is clinically appropriate, providing they give the patient sufficient safety netting advice. This advice may include ensuring patients are aware that their condition may worsen regardless of whether they take antimicrobials or not. In these circumstances other interventions such as watchful waiting or delayed prescribing may be beneficial for antimicrobial stewardship (see also section 5).

The GDG discussed the evidence that a patient's or parent's expectations may influence antimicrobial prescribing. The GDG also considered evidence that when making decisions, prescribers may not consider patient factors, such as whether the patient wants an antimicrobial.

The GDG noted that any prescribing decision should be a shared one between the patient and the health professional. The GDG acknowledged that in primary care some patients attend a consultation with a view to obtaining a prescription for antimicrobials. It may be difficult for health professionals to not prescribe antimicrobials in these situations. Nonetheless, the GDG agreed that antimicrobials should not be prescribed unless there is a clinical need. The GDG considered evidence suggesting that if patients are educated about the reasons why prescribers may decide not to prescribe an antimicrobial, patients may be happier with the decision and prescribers can refrain from prescribing antimicrobials when they are not indicated.

The GDG suggested that prescribers often consider whether the decision to prescribe is in the best interests of the patient. The GDG agreed that the health needs of a patient should be balanced with interventions to reduce antimicrobial resistance at a population level. The GDG discussed and agreed that prescribers need to consider the wider implications of antimicrobial prescribing when deciding whether to prescribe or not. The GDG discussed situations in which the patient has to decide between an invasive intervention (for example, dental work) and an antimicrobial, and agreed that the patient is more likely to choose the antimicrobial. The GDG agreed that prescribers need to discuss with the patient the benefits and harms of prescribing an antimicrobial, ensuring that enough appropriate information is discussed with the patient to allow an informed decision to be made (for example, whether prescribing an antimicrobial is just delaying a more invasive intervention that the patient will need anyway).

Clinical priorities

The GDG considered the evidence that prescribers may consider antibiotic resistance to be infrequently encountered in their practice and therefore rate this as a lower priority than day to day clinical considerations. Some questioned whether prescribing of antimicrobials is linked to antimicrobial resistance and hence poorer patient outcomes. The GDG discussed the evidence that antimicrobial resistance was perceived to be a national issue rather than local issue; GDG members further considered this in relation to the evidence that prescribers may consider antimicrobial resistance to be an issue that is not encountered in their day to day practice. The GDG concluded that educating prescribers and providing them with feedback on their own prescribing data along with local antimicrobial resistance patterns could emphasise the need for appropriate antimicrobial prescribing at a local level.

Policy and guidelines

The GDG discussed the evidence that suggested that some health professionals may feel that antimicrobial stewardship policies reduce their

freedom to prescribe, infringe on their professional judgement and do not value their intuition and experience; evidence suggested that non-compliance with policy may be related to prescriber autonomy and personal experience. The evidence also suggested that health professionals often consider their patients to be outside the boundaries of local guidelines. Therefore, the GDG agreed that non-compliance with local policies and guidelines for antimicrobial use can be a barrier to effective decision-making and prescribing. The GDG agreed that to support effective implementation health professionals should understand the rationale for having the guidelines in place and have the opportunity to be involved in developing, reviewing and implementing local guidelines.

The GDG agreed that guidelines should empower prescribers to decide whether to prescribe or not. For those conditions for which antimicrobials are frequently prescribed; local guidelines should provide information to support GPs to decide whether alternative interventions to immediate prescribing may be more appropriate (for example, delayed prescribing).

Hierarchal structures of health professions

The GDG considered the evidence suggesting that doctors' antimicrobial prescribing is governed by peer networks and hierarchies of staff. The GDG agreed that all health professionals are accountable for effective antimicrobial stewardship. Therefore all health and social care practitioners need to work together to address this important issue.

The GDG discussed evidence suggesting that senior health professionals can strongly influence the prescribing practice of junior staff and that individual teams can have patterns of prescribing. The GDG agreed that it was important to recommend involving leaders in all care settings in any antimicrobial stewardship programme because they can influence their colleagues and support appropriate antimicrobial prescribing.

The GDG discussed the issue that health professionals who review antimicrobial prescribing may find it difficult to question the prescribing practice of more senior colleagues. The GDG agreed that senior health professionals should educate members of their team about the importance of antimicrobial stewardship and should encourage an open and transparent culture, allowing prescriptions for antimicrobials to be challenged if they are not in line with local guidelines and there is no documented reason for the prescription.

Education

The GDG considered whether being unaware of or not using up-to-date antimicrobial guidelines might be a barrier to antimicrobial stewardship and making appropriate decisions about antimicrobial prescribing. The evidence suggested that undergraduate programmes do not provide enough training in antimicrobial prescribing and resistance to enable prescribers to make autonomous decisions about antimicrobial prescribing when they qualify. GDG members noted the importance for antimicrobial stewardship of prescribers having current knowledge about the management of infections to enable them to effectively prescribe according to national and local guidelines.

The GDG discussed examples of how some clinical areas (for example, surgical services) have developed networks across the country for sharing practice and experience. The GDG agreed that the evidence and their experience indicates that communicating and sharing consistent messages

about the use of antimicrobials supports the reduction of barriers to effective antimicrobial stewardship. The GDG agreed that the approaches that have been developed in areas such as surgical services could be recommended for sharing learning and experience in relation to antimicrobial resistance and antimicrobial stewardship. The GDG consequently agreed that the development of local networks could support the sharing of information relevant to antimicrobial stewardship (see also the recommendations on the medicines-related patient safety incidents in the [medicines optimisation](#) guideline (publication expected March 2015).

Antimicrobial prescribing and resistance data

The GDG considered evidence suggesting that providing more information to prescribers locally about resistance patterns could support antimicrobial stewardship. The GDG noted that antimicrobial resistance patterns vary across the country. The GDG agreed that organisations should be aware of resistance patterns in their area and of the corresponding prescribing data. Senior health professionals should be aware of these data and should ensure that these trends and subsequent actions are communicated to health and social care practitioners. The GDG also agreed that data on local resistance patterns would support education and training of health professionals. The GDG also supported data on antimicrobial resistance being available in the public domain.

Monitoring, evaluation and audit

The GDG discussed whether showing prescribers their prescribing patterns and those of their peers (for example, other prescribers in a GP practice or other practices or clinical commissioning groups) could change prescriber decision-making.

As discussed when reviewing the evidence relating to practitioner decision-making, the GDG agreed that an audit of practice would be valuable to provide feedback to prescribers about their practice. The GDG further discussed the importance of clinical audit for review of whether antimicrobial prescribing is in line with national and local guidelines. GDG members also discussed how the recording of diagnosis varies in different care settings. The GDG agreed that it is important to carry out regular audit of antimicrobial prescribing in all care settings and that to do so prescribers should document the condition being treated and maintain a record of any antimicrobial that has been prescribed.

The GDG discussed the accessibility and value of prescribing data and was aware that prescribing patterns can vary across the country. The GDG noted that detailed prescribing data on prescriptions issued in the community in England are held by the NHS Business Services Authority (NHS BSA). These data can be accessed by medicines teams in organisations responsible for commissioning services such as clinical commissioning groups (CCGs), local authorities and NHS England area teams. The data are available at individual prescriber and practice level for CCGs and local authorities and at CCG level for NHS England area teams. The GDG was aware that access to prescribing data by other organisations, such as commissioning support organisations, can be granted by the commissioning organisation, although this is not mandatory and practice is variable.

The GDG understood that the NHS BSA system was originally set up to support payment processing of NHS prescriptions. Over time the use of these data has changed and they are no longer solely used for payment purposes. Prescribing data are now used (for example, by medicines teams) to review prescribing patterns and trends. The GDG was aware that

there are limitations with these data and that some prescribing data are not always available through this system at a local level (for example, out-of-hours and dental prescribing data). This therefore represents a gap in reviewing the prescribing patterns and trends of antimicrobials.

The GDG discussed the systems and processes for documenting treatments and prescribing in dental practices. The GDG noted that in dental practices documenting interventions can be either electronic and/or paper, and not all practices use the same method. Furthermore, no reason codes exist for documenting treatment and/or diagnosis as in GP practices or hospitals. In dental practices, there are no systems for prescribing electronically or for printing out prescriptions so prescriptions continue to be hand written. The GDG was aware therefore that there is no safety-netting and the dentist needs to be aware of drug interactions, dosing or other medicines information before prescribing. Because of this variable infrastructure, there is no provision to currently support electronic transfer of dental prescriptions (electronic prescription service [EPS]) to a patient's nominated community pharmacy.

For dentists, payment processing is different to that in GP practices. There is no requirement for dental prescriptions to include information about an individual prescriber, which is why data from individual dental practices are not available from the BSA. The BSA can collate dental prescribing data in England and these are published in annual reports by the [Health and Social Care Information Centre](#). However, these data do not allow analysis of local prescribing patterns or trends; this can only be done on a countrywide basis.

Currently GP prescriber codes are linked to the BSA individual cost centre rather than that of individual prescribers (for example, locums, who are not working permanently in a location, often use a 'general' prescriber code in 1 practice for all of their prescribing). Prescribing data do not therefore always just represent the GP name assigned to that code or cost centre.

The GDG was aware that an [Information Standard](#) is being developed that supports this approach for all prescribers (titled [Prescriber ID](#)). This information standard will recommend a 'national prescriber identifier standard'. The GDG was aware that several prescriber professionals already use their professional regulatory codes when prescribing (for example, some nurse prescribers). The professional regulatory code is also used when prescriptions are issued through the [Electronic Prescriptions Service](#) (EPS) version 2. EPS enables prescribers (such as GPs and practice nurses who can prescribe) to send prescriptions electronically to a dispenser (such as a pharmacy) of the patient's choice (a nominated pharmacy). Professional regulatory identifiers are unique for each individual and cannot be transferred between people. The GDG felt that it was important for all prescribers to be able to review their own prescribing data for antimicrobials and that professional regulatory identifier numbers would support this.

In line with this work, the GDG concluded that for antimicrobial stewardship it would be beneficial for all prescribers to use their professional regulatory numbers (as well as the prescriber [cost centre] codes, where appropriate) when prescribing antimicrobials to allow for review and audit of prescribing practice.

Trade-off between

The evidence identified some barriers to decision-making in relation to

benefits and harms	antimicrobial stewardship. Some of the evidence suggested interventions to overcome these, but the interventions were not assessed for effectiveness in the studies.
Resource considerations	<p>No studies of cost effectiveness were identified for this review question. However, the evidence identified resources as being a barrier to antimicrobial stewardship. Six studies identified a lack of resources as a barrier; 5 of these were cross-sectional studies and 1 was a qualitative study using focus groups. The GDG noted that all the evidence came from a secondary care setting.</p> <p>The GDG discussed the resource barriers identified in the evidence (time, staffing, funding, technology) in relation to antimicrobial stewardship programmes. The GDG noted that these would be different in different care settings. The GDG agreed that commissioners should consider the resources needed to fund effective antimicrobial stewardship programmes. The GDG agreed that commissioners should ensure that services commissioned have effective antimicrobial stewardship programmes, which consider the monitoring of antimicrobial resistance, the resources needed and how a programme will support antimicrobial stewardship across care settings. The GDG agreed that it is important for commissioning and provider organisations to collaborate and consider the role of individuals in an antimicrobial stewardship programme, including clear lines of responsibility and accountability.</p> <p>While continuing to consider resources as a barrier, the GDG discussed whether hospital managers are aware of the importance of antimicrobial stewardship and the possible cost saving an effective antimicrobial stewardship programme can have.</p> <p>The GDG was aware of the international and national importance of effective antimicrobial stewardship in reducing antimicrobial resistance and agreed that hospital managers should consider allocating appropriate resources to ensure effective antimicrobial stewardship programmes are implemented.</p> <p>The GDG also agreed that commissioners should identify the resources needed to provide effective antimicrobial stewardship programmes in terms of time, funding and staffing, including unscheduled and routine care.</p>
Quality of evidence	<p>The GDG noted the lack of any RCTs identified for this review and that the included evidence for this question was considered to be of very low quality. The evidence reviewed related to secondary care and was taken from care settings in Europe, the USA and Australia.</p> <p>The GDG members considered that the evidence reviewed was relevant to the review question but that developing recommendations would require considerable input from them and consensus decisions.</p>
Other considerations	<p>Antimicrobial stewardship programmes</p> <p>The GDG was aware that antimicrobial stewardship programmes covered a wide range of activities and therefore the barriers identified by the individual studies related to different types of programme. The GDG discussed the barriers that were identified in the evidence to antimicrobial stewardship programmes. GDG members considered barriers such as prescribing practice being influenced by other colleagues, perceptions that a patient's or a parent's expectation is to receive antimicrobials, or the competing priorities for prescribers' time. This led the GDG to discuss what an ideal programme/team for antimicrobial stewardship might consist of. The GDG agreed that an antimicrobial stewardship programme is likely to include</p>

different processes, resources and structures depending on the setting or the health or social care practitioners involved in the programme (for example, prescribers, commissioners or social care staff). The GDG concluded that an effective antimicrobial stewardship programme should include the following outcomes:

- monitoring and evaluating antimicrobial prescribing (for example, reviewing how antimicrobial prescribing relates to local resistance patterns)
- providing regular feedback to prescribers in all care settings about their antimicrobial prescribing (for example, by using professional regulatory numbers for prescribing as well as prescriber [cost centre] codes)
- providing regular feedback to prescribers in all care settings about patient safety incidents related to antimicrobials, including hospital admissions for rare or serious infections or associated complications (for example, mastoiditis, pyelonephritis, brain abscess, quinsy, empyema, meningitis or *C. difficile* infections) thought to be linked to a lack of or inappropriate antimicrobial prescribing
- providing education and training to health and social care practitioners about antimicrobial stewardship and antimicrobial resistance.

The GDG discussed how some of the barriers identified in the evidence could impact on the implementation of an effective antimicrobial stewardship programme, including how a programme could be delivered in practice. The GDG agreed that any approach for implementing an effective antimicrobial stewardship programme needs to consider how to work across all care settings where antimicrobials may be prescribed. It was agreed that primary and secondary care organisations need to work together to ensure that consistent messages about antimicrobial use are given. To assist with this the GDG recommended establishing a wider antimicrobial stewardship team that works across all care settings.

Communication

The GDG was aware that it is important to inform the patient about who to contact if they have questions or concerns about the antimicrobial they have been prescribed. The GDG heard that it can be particularly difficult for a dentist to advise a patient with a dental infection on appropriate dental care if a GP has already prescribed an antimicrobial. Similarly, if the patient is prescribed an antimicrobial by a dentist, it can be difficult for a GP to offer advice if approached by the patient. The GDG concluded that it is important to share relevant information about antimicrobials. When sharing information, health and social care practitioners should take into account the 5 rules set out in the Health and Social Care Information Centre's ['A guide to confidentiality in health and social care'](#) (2013).

The GDG discussed the evidence suggesting that improving existing collaborations may further improve judicious antimicrobial use. The GDG discussed the need for clear communication and collaboration between different health and social care settings to ensure that all health and social care practitioners support the same messages. The GDG considered that the evidence alongside their experience indicated the need for clear communication between care settings. The GDG had specifically considered this in regard to clear communication between secondary and primary care for patients who have undergone surgery and may be at increased risk of developing wound infections. The GDG was aware that patients who develop infections after surgery may visit the GP for advice. However, the GDG agreed that it may be more appropriate for the patient to contact the team that carried out the surgery. The GDG agreed that it was

therefore important for commissioners and providers to agree a local process/patient pathway for the management of post-operative infections. In relation to antimicrobial stewardship, the GDG felt that it was important to consider review with the patient's surgical team for surgical site infections (especially for impact surgery). The GDG discussed how this might be done (for example, through a dedicated contact number or follow-up by the surgical team).

The GDG was aware of the NICE guideline on [surgical site infection](#) (CG74) and discussed the importance of including information in patient pathways.

The GDG agreed that this could be extrapolated to general patient pathways that involve the management of infections when a patient moves from one care setting to another. These pathways should include advice about who is the most appropriate health professional a patient should contact if they have concerns. The GDG discussed the challenges around communication and agreed that colleagues should endeavour to communicate consistent messages about antimicrobial stewardship.

1 **7.7 Recommendations and research recommendations**

2 See section 4.2 for a list of all recommendations and appendix F for a summary of the
3 evidence linking the recommendations.

8 Timely adoption and diffusion of a new antimicrobial

8.1 Introduction

In 2014 the UK government announced a [wide ranging review](#) of antimicrobial resistance. The review will establish a plan for encouraging and speeding up the discovery and development of new generations of antibiotics, and will include:

- ‘the development, use and regulatory environment of antimicrobials, especially antibiotics, and explore how to make investment in new antibiotics more attractive to pharmaceutical companies and other funding bodies
- the balance between effective and sustainable incentives for investment, and the need to conserve antimicrobial drugs so they remain effective for as long as possible
- how governments and other funders can stimulate investment in new antimicrobials and timeframes and mechanisms for implementation
- increasing international cooperation and support for action by the international community, including much closer working with low and middle income countries on this issue’.

The House of Commons Science and Technology Committee report [Ensuring access to working antimicrobials](#) sets out the challenges for developing new antimicrobials and asks how organisations can re-engage in research and development of new antimicrobials for the future. The report also highlights the economic issues surrounding antimicrobial resistance. The [UK government response](#) to this report details further the action being taken to address antimicrobial resistance in this area.

In 2011 the [annual report of the Chief Medical Officer, volume two, 2011: Infections and the rise of antimicrobial resistance](#) stated that ‘the supply of new classes of antimicrobial agents for future use has slowed over the last few decades in contrast to drug development for other conditions.’ The report goes on to list a number of factors that limit the economic incentives to the development of new antimicrobials these include:

- ‘Antimicrobial agents are used sparingly and for short duration.
- Over time, they are subject to diminished efficacy due to the development of antimicrobial resistance.
- Sometimes they are withheld for the future, limiting the profitability of a fixed term patent.’

The Department of Health has previously set out the need ([Innovation, health and wealth, 2011](#)) for the improved ‘adoption’ (defined as ‘putting a new idea, product or service into practice’) and ‘diffusion’ (defined as the systematic uptake) of new interventions within the NHS in England. This section is concerned with ensuring that there is appropriate adoption and diffusion of new antimicrobials, that any diminished efficacy is monitored and that any restriction on prescribing is clinically justified.

8.2 Review question

What interventions, systems and processes are effective and cost effective in the responsible, timely adoption and diffusion, where appropriate, of a ‘new’ antimicrobial^c into the National Health Service (NHS)?

- 1 The term 'new' antimicrobial includes:
- 2 • a new antimicrobial
 - 3 • a newly marketed formulation of an existing antimicrobial and/or
 - 4 • an antimicrobial that is licensed but not available on the NHS.

5 **8.3 Evidence review**

6 **8.3.1 Clinical evidence**

7 A systematic literature search was conducted (see appendix C.1.2.4) and identified 2489
8 references. After removing duplicates, the references were screened on their titles and
9 abstracts to identify studies as being relevant for inclusion in the review. No references were
10 obtained and reviewed against the inclusion and exclusion criteria as described in the review
11 protocol for the timely adoption and diffusion of new antimicrobials into the NHS (appendix
12 C.2.4). However, 7 partially applicable non-research articles were obtained for background
13 information. These provided information on organisational approval processes for new
14 antimicrobials, implementation planning for the introduction of a new antimicrobial and
15 decisions to restrict access to a new antimicrobials (see section 9 [references] and table 18
16 for a summary of the key themes).

17 An additional interrupted time series study was identified by the GDG as being suitable for
18 inclusion (McNulty 2011) and full text of this article was obtained and included.

1

Table 16: Summary of included studies

Study	Population	Intervention	Comparison	Key critical and important outcomes
McNulty (2011) ¹ <i>England</i>	Not specified	A change in antibiotic susceptibility reporting	Information recorded in the control period	Volume of antimicrobials prescribed Laboratory reporting – for example, what sensitivities are shown, the order of the antimicrobials to prescribe, hiding of specific antimicrobials Uptake over time by geographical area

¹ *Interrupted time series analysis*

1 **8.3.2 Additional evidence**

2 After appraisal of the published literature, the NICE project team determined that there was
3 insufficient published evidence to answer the review question and address the key issues
4 identified by the GDG.

5 The GDG reviewed the evidence and determined that the most appropriate method to
6 address the gap was to undertake a call for evidence from the NHS service.

7 The NICE project team opened a call for evidence in line with section 8 of the [Interim](#)
8 [methods guide for developing good practice guidance](#). Questions were written and agreed by
9 the GDG. The NHS was asked to respond to the questions.

10 Eighty-two completed submissions were received from organisations across England, Wales
11 and Scotland. The evidence was appraised by the NICE project team and reviewed by the
12 GDG. Appendix G lists those organisations that submitted written evidence.

13

1

Table 17: Summary of Call for Evidence Information

Question	Summary of respondents information
Does your organisation have a process for the adoption of new medicines?	<p>All respondents had a process in place for the adoption of new medicines. Most commonly this was through review by a drugs and therapeutics committee (DTC) although other specific committees were named as being a part of the adoption process: medicines management committees, joint formulary committee and therapeutic advisory services. All had similar submission and approval processes to the DTC.</p> <p>Some organisations did not state what prompted a committee to look at a new medicine, but where this information was provided it was most often in relation to a doctor or health professional with an interest in using the medicine submitting evidence for the committee to consider.</p> <p>There was some evidence of sequential approval processes being in place (that is, first 1 committee giving approval and then another) particularly where decisions were being taken across primary and secondary care. It was reported that the time taken for this approval to use a new medicine was extended as a result.</p>
Does your organisation have a different process for the adoption of new antimicrobials? If so how and why?	<p>Around half of the organisations responding to the question stated that their process for considering the adoption of 'new' antimicrobials was no different to that used for any other new medicine. Those that differed most often reported that an antimicrobial group (for example an antimicrobial stewardship, infection control or clinical speciality group) would review the application before sending it to the approving committee and make recommendations as to whether to adopt the new antimicrobial and any relevant conditions for use. The rationale given for using this process was often that the committee lacked the breadth of skills within its membership to consider all the relevant factors related to new antimicrobials.</p> <p>The committee membership (where described) most often comprised:</p> <ul style="list-style-type: none"> • a consultant microbiologist • an infectious diseases consultant • an antimicrobial pharmacist. <p>In some cases there was representation on the group from outside of secondary care settings. The view from primary care respondents was that considering the use of new antimicrobials is generally led by secondary care. The factors considered by these groups (in addition to cost and effectiveness considered by the approving committee) were stewardship issues relating to:</p> <ul style="list-style-type: none"> • the need for monitoring of use of the new antimicrobial

Question	Summary of respondents information
	<ul style="list-style-type: none"> • control of prescribing (restrictions on use) • safe and effective introduction of the new antimicrobial • local need for the new antimicrobial • local patterns of antimicrobial resistance • place of the new antimicrobials in therapy. <p>One other process mentioned was the need to bypass all approval mechanisms for new antimicrobials when clinical expediency was required. A few organisations stated that any urgently required new antimicrobials can be used and approved via retrospective submission to the approving committee.</p>
<p>How do you use the antimicrobial once adopted? For example, do you restrict prescribing or is it freely available?</p>	<p>No respondent thought that new antimicrobials should be freely available to prescribe by any prescriber (unless it was a new formulation of an older, established medicine). Restricting the use of new antimicrobials was likely to be dependent on: the individual antimicrobial, any concerns regarding its introduction and its place in therapy with more restrictions being placed upon 2nd, 3rd and last line antimicrobials. Cost of the new antimicrobial was also an important factor in placing restrictions on use. The types of restriction most often discussed by respondents were:</p> <ul style="list-style-type: none"> • a prior approval process with permission sought from a consultant microbiologist or similar, • use being limited to certain specialities (for example intensive care units) • use limited to specialist initiation • use requiring post-prescription specialist review • local restriction of new antimicrobials was communicated to prescribers through the use of guidelines, formulary and clinical commissioning group prescribing recommendations in primary care.
<p>Do you produce an implementation plan to support appropriate prescribing once it is approved for use?</p>	<p>Most secondary care respondents had some form of implementation plan to support the appropriate prescribing of new antimicrobials once they are approved, however 15 secondary care respondents stated that they do not have implementation plans. For respondents from primary care only 2 of the respondent organisations stated that they would have a plan, even then this only related to updated routine processes such as guidelines or formularies. The commissioning support units stated that they would put plans in place (in cooperation with secondary care) if this was deemed appropriate.</p> <p>The most commonly cited methods of implementation which were planned for new antimicrobials in secondary care were:</p> <ul style="list-style-type: none"> • alerts via e-mail and through intranet to prescribers • new or updated guidelines for prescribing and formulary

Question	Summary of respondents information
	<ul style="list-style-type: none"> • individual peer to peer advocacy as required • guidance specific to new antimicrobial for prescribers • educational interventions for appropriate speciality teams, informal teaching on ward rounds or post antimicrobial audit educational visits • laboratory support for prescribers.
If so what criteria does this include?	<p>Where implementation plans are used common information for prescribers included:</p> <ul style="list-style-type: none"> • when to use a new antimicrobial • any criteria (illness severity score) for use • the safety profile of the new antimicrobial • dose, dose adjustment for concomitant illness (for example, renal failure), duration of course length and review dates • any advantages or disadvantages compared to other antimicrobials • options for allergy status • any other licensing information • any local restrictions (for example, prior approval, monitoring, specialist initiation).
What is the timescale from adoption to prescribing? Are there any barriers to this happening and if so, what are they?	<p>Most respondents from secondary care reported fairly rapid timescales from adoption to prescribing (immediately available or just days before first use) with many saying the main barriers to prescribing (apart from any prescribing restrictions applied during approval) or use were due to availability, ordering or supply.</p> <p>Many respondents both in primary and secondary care stated that barriers causing the main delays were pre-adoption (committee processes and bureaucracy) as these processes were reported to take up to 6 months (from the time a doctor or health professional submits an application of interest and supporting evidence through to approval and first use due to multiple, sequential committee processes).</p> <p>However, a number of respondents noted that prescribers were often reluctant to change their practice, perhaps due to lack of prescriber awareness or experience with the new medicine. Some respondents reported that it took a while to update formulary and guidelines or to otherwise cascade information about the availability of the new antimicrobials to prescribers.</p> <p>Another identified barrier to the use of a new antimicrobial was funding. In a small number of cases in secondary care, internal directorates needed to determine the resource impact on their budget before prescribing a new antimicrobial, particularly for expensive</p>

Question	Summary of respondents information
	antimicrobials. Another identified a funding barrier through payment by results (PbR), a mechanism through which NHS Trusts in England are paid for care they deliver. This includes a list of specific medicines that are excluded from the PbR mechanism; clinicians and provider organisations may delay use whilst seeking clarification over funding from commissioners.
When an antimicrobial has been approved for use locally, what monitoring and evaluation is used, if any, to ensure appropriate use? Please explain your process.	<p>There was variation in monitoring and evaluation processes used to assess the impact and use of new antimicrobials. Some organisations responded that they had no systems in place, in 1 response it was stated that it was not applicable to the organisation (a primary care provider organisation).</p> <p>Other, predominantly secondary care, organisations had systems in place although there was a wide variation in the number of processes used between different organisations. They included:</p> <ul style="list-style-type: none"> • review of medicines use (case note, prescription or electronic prescription chart review) after an ‘appropriate period’ based on frequency of use • restricted, alert or off-formulary antimicrobials use reviewed by either an antimicrobial pharmacist or an antimicrobial stewardship team with feedback to the prescriber • cost and resource review of new antimicrobials at various time points • point prevalence audit of all or new antimicrobials use • daily ward round review of antimicrobials use by an antimicrobial pharmacist or microbiologist • education and training for clinical pharmacists to ensure day-to-day coverage on the wards with stewardship • Defined Daily Dose (DDD) was the most commonly cited monitoring measure.
Has the incidence of resistance changed as a result of your process? If so, to what degree and how was this measured?	<p>No respondent organisation has measured changes in resistance resulting from changes in processes for approval of new antimicrobials. Additionally where resistance data has been collated over time respondents state that it would be very difficult to isolate the effects a single process such as an approval process in terms of resistance to a new antimicrobial, as the organisations will have multiple processes of stewardship and infection control running concurrently.</p> <p>In general more monitoring was being conducted in secondary care.</p> <p>Only 2 organisations (both NHS Trusts in Scotland) suggest that processes are having an effect, in both cases the respondents cite reduced resistance rates from restriction of antibiotics (such as classes of cephalosporins). However, these are existing antimicrobials not new antimicrobials and so the responses do not directly answer the question.</p>

Question	Summary of respondents information
<p>What barriers do you think exist for the introduction of a new antimicrobial? Please give brief examples</p>	<p>Most respondents cited the cost of new antimicrobials as a barrier to its introduction. New medicines cost almost invariably more than the ones they are meant to replace or supplement (examples given commonly included linezolid and fidaxomicin). Several respondents state they use these newer antimicrobials only in specific cases (such as high risk cases or older people) due to cost considerations.</p> <p>The respondents also cited a concern about a lack of evidence for some new antimicrobials. This was a real concern for several respondents as they state that clinicians are reluctant to initiate the use of new antimicrobials early if there is insufficient data on safety. Dosing and safety was felt to be lacking for particular populations such as children, neonates and older people, which arguably make up a large proportion of those receiving antimicrobial therapy. Another issue was the length of time it takes for clinical effectiveness data to be published (an example given was daptomycin which the respondent stated took several years to demonstrate clinical efficacy). A number of respondents expressed concerns about the lack of evidence on the risk of resistance and healthcare associated infection associated with newer antimicrobials.</p> <p>Another concern was that newer antimicrobials may not have a clinical advantage over current therapies (an example given was fidaxomicin versus vancomycin for the treatment of <i>C. difficile</i>) and often the newer therapy may come at a substantially higher cost than the current therapy.</p> <p>A further concern regarding the effectiveness of new antimicrobials was raised as 1 respondent who noted that there was reluctance from prescribers to replace broad spectrum antimicrobials with narrower spectrum antimicrobials, which were perceived as potentially less effective. On a broader aspect of prescriber awareness many respondents stated that prescriber awareness and experience of newer antimicrobials (several examples such as, pivmecillinam, temocillin, caspafungin and voriconazole [versus ambisone] in the treatment of an unspecified haematology condition) was an issue.</p> <p>Concern was raised by respondents about the licensed formulations of antimicrobials available for treatment of certain conditions (commonly the example of the formulation of fosfomicin available for the treatment of extended spectrum beta-lactamase urinary tract infections).</p> <p>For a new antimicrobial many respondents identified the time from a marketing authorisation being issued to the time of local approval and adoption for use as being a barrier, with time delays of up to 6 months before approval.</p> <p>A point was raised by 1 respondent about the effects of restricting access to new antimicrobials for the purposes of stewardship, which</p>

Question	Summary of respondents information
	<p>relates to the selection of particular patients in whom these locally restricted antimicrobials are subsequently used. Typically valuable new antimicrobials are as has been discussed restricted for use. The respondents report that restrictions are mainly put in place for antimicrobial stewardship reasons. However the respondent states that these restricted antimicrobials end up being used in selected clinical cases or certain specialities because these patients are unresponsive to existing therapy and/or have a poor prognosis. The respondent felt that this may lead to unrepresentative views of the effectiveness of the drugs and their place in therapy. The populations for which an antimicrobial may be restricted may not be the population in which they were originally studied leading to variation in both effectiveness and cost effectiveness of their use in practice.</p> <p>A small number of respondents discussed the impact of delays in the national approval (by NICE or Scottish Medicines Consortium) and/or licensing delays from the European Medicines Agency (EMA) or the Medicines and Healthcare products Regulatory Agency (MHRA).</p>
<p>When considering whether to adopt a new antimicrobial, to what extent are patient / carer views considered?</p>	<p>Most respondents stated that their processes for the approval of new antimicrobial took account of patient factors such as acceptability of the new antimicrobial, any side effects or safety data concerning the new antimicrobial, whether the new antimicrobial offered improved convenience (for example a once daily dose compared to three doses of an existing antimicrobial) and any issues with adherence to the new antimicrobial.</p> <p>Most respondents stated that patient views on the approval of specific new antimicrobials were not considered, however a small number stated that patient representatives or lay members were part of their drugs and therapeutics committee.</p>
<p>If an antimicrobial has been 'rejected for routine use' or restricted, how is this decision reviewed, particularly considering antimicrobial availability?</p>	<p>Most respondents reported that they had formal processes for reviewing decisions regarding new antimicrobials that have been rejected for routine use or restricted. However, there was a fair amount of variation in practice from the responses given to the question and a few respondents stated that decisions were not reviewed or there was no formal process for review in place.</p> <p>The most commonly cited reasons for conducting a review were to assess usage as part of ongoing stewardship processes, a committee review prompted by a consultant, pharmacist or prescriber request, a review prompted by new evidence, a review prompted by formulary or guideline review or planned reviews at 1, 2 or every 3 years.</p>

1

Table 18: Key themes matrix (Summary of non-research background articles)

Study	Organisational approval processes for new antimicrobials	Implementation planning for the introduction of a new antimicrobial	Decisions to restrict access to a new antimicrobial
Bertino (2001) <i>USA</i>	Formulary decisions: <ul style="list-style-type: none"> • route of administration • contraindications • cautions • adherence • dose adjustment • tolerability (adverse effects) • drug interactions 		Issue of high level cross resistance (such as resistance to new antimicrobial because of resistance to older antimicrobials of the same class)
Keegan (2001) <i>USA</i>	Formulary decisions: Input from experts with knowledge of local patterns of resistance needed.	Rules for stopping therapy (when no diagnosis of infection is made)	
Mason (2008) <i>UK</i>		Suggests GP attitude to guidance improving, NICE appraisal presented in isolation has little effect on uptake, additional sources needed. Uptake of new antimicrobials is a gradual and cumulative process. PCT prescribing advisors help reinforce national guidance, but not all GPs seek advice from them. Low prescribers of new antimicrobials seek advice from others, peer reviewed and other sources (pharmaceutical representatives). Multifaceted interventions appear to work better in increasing uptake but the background (knowledge, beliefs, attitudes and behaviour) is complex. Safety of new [antimicrobial] medicines is the prime concern of prescribers.	Complexity and safety of hospital initiated prescribing (communication barriers)
Nathwani (1999) <i>UK</i>	Formulary decisions: <ul style="list-style-type: none"> • Costs (not just acquisition cost) i.e. monitoring costs, likely subsequent 		

Study	Organisational approval processes for new antimicrobials	Implementation planning for the introduction of a new antimicrobial	Decisions to restrict access to a new antimicrobial
	<p>outcomes and adverse events costs.</p> <ul style="list-style-type: none"> • Effectiveness pharmacological efficacy (in vitro). • Patient compliance. • Population in which the new [antimicrobial] medicine or specific formulation may be used. • Input from community practitioners and patient representatives in formulary decision making. 		
Pujol (2013) <i>Spain</i>	<p>Formulary decisions:</p> <ul style="list-style-type: none"> • Input from experts with knowledge of local patterns of resistance needed. • Indication for use • Population in which the new medicine or specific formulation may be used. • Effectiveness pharmacological efficacy (in vitro). • Safety information • Costs • Place in therapy 		Antimicrobials unable to provide additional benefits over existing therapies should not be approved.
Raber (2010) <i>USA</i>	<p>Formulary decisions:</p> <ul style="list-style-type: none"> • Effectiveness pharmacological efficacy (in vitro). • Safety information • Costs (not just acquisition cost) i.e. monitoring costs, likely subsequent outcomes and adverse events costs. 	<p>Risk assessment and risk management strategies for use of potentially useful but ‘problematic drugs’.</p> <p>Systems and processes should be in place to allow the prescription of non-formulary drugs when clinical situation dictates this necessity.</p> <p>Managed introduction based upon the amount of education or pre-introduction work (protocols, pre-approval processes, drug safety</p>	Prior approval for medicines with greater risks or limited to certain specialities or settings.

Study	Organisational approval processes for new antimicrobials	Implementation planning for the introduction of a new antimicrobial	Decisions to restrict access to a new antimicrobial
Tam (2006) <i>USA</i>	Formulary decisions: <ul style="list-style-type: none"> • Input from experts with knowledge of local patterns of resistance needed. • Place in therapy • Dosing regimen • Costs (not just acquisition cost) i.e. monitoring costs, likely subsequent outcomes and adverse events costs. 	processes) that needs to be undertaken.	

1 **8.3.3 Health economic evidence**

2 No health economic evidence was identified for this review question.

3 **8.4 Evidence statements**

4 **8.4.1 Clinical evidence**

5 Evidence from 1 prospective interrupted time series study of changes made to the reporting
6 of microorganism sensitivity in urine samples showed a significantly reduced volume of
7 prescribing for the antimicrobial that was no longer reported on. There was a significant
8 increase in the volume of prescribing for the antimicrobial that was reported on. No clinical
9 outcomes were reported.

10 **8.4.2 Call for evidence**

11 Organisations have processes for the approval of new medicines, although this is not always
12 a single approving body (for example, a drugs and therapeutics committee) that covers
13 primary and secondary care settings. This can lead to delays in the use of a new medicine
14 while it is being approved by a number of committees.

15 Most organisations take into account patient factors such as adherence, safety and
16 tolerability when considering a new antimicrobial. However, few organisations involve a
17 patient representative or lay member in the approval process.

18 Most organisations have a process for reviewing decisions not to approve new medicines for
19 routine use. However, there is variation in the criteria for staging a review (for example,
20 clinician request, new evidence becoming available, routine review or a review of local
21 formulary and guidance).

22 Some organisations require specialist antimicrobial input into decisions about the approval of
23 new antimicrobials. In some cases, an antimicrobial stewardship team assesses a new
24 antimicrobial before an approving committee makes a decision. It has been reported that
25 although this slows down the approval process and delays adoption, it results in more
26 appropriate decisions.

27 No organisational response suggested that a new antimicrobial should be freely available to
28 prescribers and patients without some form of restriction. Most organisational responses felt
29 that restrictions placed on use of a new antimicrobial would be specific to the antimicrobial
30 itself; however there was variation in the type of restrictions applied by organisations.

31 There was a wide variation in the planned and supported introduction of new antimicrobials,
32 particularly between primary and secondary care. Some organisations do not plan and
33 manage the introduction of new antimicrobials, and this was more common in primary care.
34 The interventions used in primary care were passive (for example, guidelines update) rather
35 than the much more varied and active interventions like education and peer to peer advocacy
36 used in secondary care.

37 Organisations identified a number of barriers to the rapid adoption of new antimicrobials.
38 These included organisational processes (for example, the need for multiple committees to
39 approve a new medicine), prescriber inertia (linked to the delay between an approving
40 committee approving a new antimicrobial and providing support to prescribers with updated
41 guidance and formulary) and internal and external funding agreements (departmental funding
42 or funding for Payment by Results [PbR] excluded medicines).

1 There was a wide variation in the amount of monitoring undertaken to ensure that new
 2 antimicrobials are being used appropriately (in line with local guidance and formulary). Less
 3 activity was reported in primary care. There was wide variation in the processes used for
 4 monitoring.

5 No organisation had noted a change in resistance related to the processes used to approve,
 6 implement or monitor the use of a new antimicrobial.

7 Organisations identified a number of barriers to the adoption and diffusion of new
 8 antimicrobials. These included cost of the new medicine, a lack of evidence of effectiveness
 9 and, in particular, a lack of demonstrated advantage over other available antimicrobials,
 10 delays in local or national approval, and the effect of local restrictions on use.

11 8.4.3 Economic evidence

12 No health economic evidence was identified for this review question.

13 8.5 Evidence to recommendations

14 **Table 19: Evidence to recommendations**

Quality of evidence	<p>The GDG was aware that the McNulty (2011) study was a well conducted interrupted time series study of alterations made to microbiological sensitivity tests. However, due to the lack of concurrent control it was less robust than evidence from a randomised controlled trial.</p> <p>The call for evidence provided the GDG members with information from responding organisations on variation in practice. Information was not analysed quantitatively but was thematically analysed and presented to the GDG to help inform their discussions. The GDG was aware that the quality of evidence was very low from both the call for additional evidence to examine the variation in current practice and the background papers from which key themes were extracted.</p>
Trade-off between benefits and harms Organisational approval processes for new antimicrobials	<p>Decision-making bodies</p> <p>Decisions relating to new medicines for local approval and inclusion within a local formulary are generally made by a formally constituted decision-making group. The name of the group and its relationship with other local policy development groups varies (see the NICE guideline on Developing and updating local formularies). Examples of local formulary decision-making groups include trust formulary groups, drug and therapeutics committees, interface formulary groups and area prescribing committees.</p> <p>The GDG discussed the barriers to the adoption and diffusion of new antimicrobials described in the call for evidence. The GDG agreed that the main barrier was a delay in the adoption and diffusion of new antimicrobials caused by the time taken for an organisation's decision-making body to approve a new medicine. This was particularly noticeable when multiple decision-making processes were used (for example, separate decision-making bodies in secondary and primary care).</p> <p>The GDG inferred from evidence from the call for evidence, that the decision-making process for new antimicrobials needs to cover different care settings (for example, primary and secondary care) to minimise delay and maximise awareness and collaboration in the adoption and diffusion of new antimicrobials.</p>

The GDG concluded that organisations should use an existing local decision-making group (for example, a 'drug and therapeutics committee', 'area prescribing committee' or 'local formulary decision-making group') to consider the introduction of new antimicrobials locally. The group should work across different care settings and other local organisations to minimise the time to approval.

Horizon scanning

The GDG discussed the need for proactive identification of new antimicrobials before they receive marketing authorisation and agreed that to minimise delays in approval, decision-making bodies should proactively undertake horizon scanning to identify new antimicrobials coming through the market authorisation process. The GDG agreed that decision-making bodies should take note of advice or recommendations from national or regional antimicrobial stewardship bodies (for example, NICE and the [Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection](#) [ARHAI]), when considering decisions about new antimicrobials.

The GDG concluded that organisations should establish processes for reviewing national horizon scanning (for example, the NICE forward planner and the National Institute for Health Research Horizon Scanning Centre) to allow for planning of the launch of new antimicrobials.

Expert review of new antimicrobials

The GDG was aware from the call for evidence that some health and social care organisations considered that there was benefit in having a separate antimicrobial stewardship group to review all applications for the use of new antimicrobials.

The GDG discussed and agreed that a standing committee of experts was not a good use of existing resources for organisations given the small number of new antimicrobials becoming available for use in the UK. The GDG agreed that adding another committee into the approval process may delay the assessment of new antimicrobials by a decision-making body.

The GDG further discussed whether all health and social care organisations would have access to specialist advice from an antimicrobial stewardship expert, particularly in smaller organisations. The GDG agreed that health and social care organisations without access to specialist advice should consider using specialists who already support other local decision-making bodies. Organisations should consider developing joint processes to avoid duplication of work and reduce resources needed.

The GDG also concluded that decision-making bodies should co-opt members with expertise in antimicrobial stewardship to existing decision-making groups when considering whether to approve the introduction of a new antimicrobial locally.

The GDG discussed who should be included in the decision-making process for a new antimicrobial. The GDG agreed that in addition to a consultant microbiologist and an antimicrobial pharmacist, this may include:

- a community practitioner
- someone with commissioning responsibility

	<ul style="list-style-type: none"> • an infectious diseases specialist (perhaps participating on a wider locality basis) • a paediatrician with expertise in infections/ microbiology if the new antimicrobial is for use in children. <p>What should be reviewed by the decision-making body?</p> <p>The GDG agreed that decision-making bodies should follow the criteria for decision-making set out in the NICE guideline on developing and updating local formularies.</p> <p>The GDG, based on a discussion of the information received in response to the call for evidence and other summary articles (see tables 17 and 18), concluded that because there are features that are unique to antimicrobials (emergence of resistance associated with use), decision-making bodies and the co-opted experts reviewing a new antimicrobial should also consider:</p> <ul style="list-style-type: none"> • the need for the new antimicrobial • the population in which it will be used • the specific organisms or conditions for which it will be used • dose, dose frequency, formulation and route of administration • likely tolerability and adherence • any drug interactions, contraindications or cautions • local patterns of resistance • whether use should be restricted and if so, how use will be monitored • any additional monitoring needed • any urgent clinical need for the new antimicrobial • any implementation planning for the new antimicrobial. <p>Reviewing and updating the need for a new antimicrobial</p> <p>The GDG discussed what should prompt a review if a decision-making body has not approved a new antimicrobial for routine use. The GDG agreed that in addition to the criteria for review set out in the NICE guideline on developing and updating local formularies the following reasons should prompt a new review:</p> <ul style="list-style-type: none"> • new evidence or surveillance data • new or increased use of the new antimicrobial outside of formulary or guidelines monitored as part of ongoing stewardship processes • a review and update of a formulary or guideline • a consultant, pharmacist or prescriber request. <p>The GDG found evidence from the call for evidence that suggested that planned reviews at 1, 2 and 3 years could be useful. However, the GDG discussed and agreed that the resource implications for doing this meant that the frequency for review should be determined by local decision-making groups.</p>
Trade-off between benefits and harms for decisions to restrict new antimicrobials	<p>Decision-making bodies restricting the prescribing of new antimicrobials</p> <p>The GDG members considered whether restricting the prescribing of certain antimicrobials could be an approach to support antimicrobial stewardship. The GDG reviewed examples submitted of specific antimicrobials being restricted in secondary care. The GDG considered whether this could also apply to primary care, and agreed that the systems and processes in place for primary care prescribing would not allow such restriction, unless</p>

individual prescriptions could be traced back to an individual prescriber. Primary care prescribing data are only accessible approximately 10 weeks after dispensing.

Mechanisms for restricting prescribing

The GDG was also aware from the call for evidence and the articles that provided background information, that there are a number of options for restricting the prescribing of certain antimicrobials in secondary care. For example:

- requirements for prescribers to have prior approval before prescribing
- restricting prescribing to certain specialists
- restricting prescribing to specific settings or patient populations.

Rationale for restricting prescribing

The GDG discussed the risks and benefits in the examples given by organisations for restricting the prescribing of certain antimicrobials.

The GDG was aware that cost was a major factor in the restriction of newer antimicrobials. From the experience of GDG members, restrictions based on cost alone have led to potentially sub-optimal antimicrobials being used over more expensive, more efficacious antimicrobials. The GDG agreed that cost alone should not normally be used by decision-making bodies as a rationale for restricting the use of new antimicrobials.

The GDG discussed whether the prescribing of new antimicrobials should be restricted for the purpose of antimicrobial stewardship. The GDG agreed that in some cases restriction may help to assess any emergence of resistance or high level cross resistance (possible resistance to the new antimicrobial due to resistance to older antimicrobials of the same class). In addition the GDG agreed that restriction of prescribing may allow control over new antimicrobials that have increased clinical risk associated with their use.

The GDG discussed the impact of delaying the adoption and diffusion of newer antimicrobials by restricting prescribing. The call for evidence revealed concerns that restriction of prescribing of new antimicrobials to selected populations may increase the emergence of antimicrobial resistance. For example use in:

- patients with infection unsuccessfully treated by first-line therapy
- patients infected with resistant organisms
- patients who are immunocompromised.

The GDG agreed that there is a lack of evidence in relation to these concerns. However, the GDG agreed that by restricting the prescribing of a new antimicrobial to a specific population, unless the population is the same as that in the study, may lead to different outcomes of effectiveness and cost effectiveness to those found in the study. In addition the GDG agreed that such restrictions on a new antimicrobial may affect its perceived effectiveness by clinicians, leading to variation in use. The GDG agreed that decision-making bodies need to take account of any potential risks as well as the benefits of restricting the prescribing of antimicrobials.

The GDG concluded that when decision-making bodies decide to restrict access to a new antimicrobial, the rationale for the restriction, the nature of restriction and which decision-making body has assessed the need for the

	<p>restriction should be documented and made available publicly. The GDG also concluded that the decision-making body should consider regularly reviewing the restriction to determine if the restriction is still appropriate.</p> <p>Risk of restriction of prescribing across care settings</p> <p>The GDG discussed whether there were any clinical risks associated with restricting the use of new antimicrobials, particularly in cases where restricted use of a new antimicrobial was started in secondary care but then continued in primary care. In primary care, practitioners may have little or no experience in using the antimicrobial. The GDG agreed that there was little evidence available on which to make a judgement about the clinical risks of restriction but agreed that it was a potential safety issue in practice.</p> <p>The GDG therefore concluded that decision-making bodies should consider assessing the benefits and risks of restricting the use of a new antimicrobial and take into account the impact of different care settings.</p>
<p>Trade-off between benefits and harms for implementation planning for the introduction of a new antimicrobial</p>	<p>Implementation planning</p> <p>The GDG were aware from the call for evidence that there is variability in practice for the planned introduction a new antimicrobial. Although evidence was limited as to effectiveness, the GDG agreed that a consistent approach to this would reduce the variations between organisations for the time taken to adopt new antimicrobials. The GDG concluded that decision-making bodies should consider planning for the timely introduction, adoption and diffusion of a new antimicrobial.</p> <p>The GDG discussed and agreed that organisations should have processes in place to review national horizon scanning (for example, the NICE forward planner and the National Institute for Health Research Horizon Scanning Centre) to allow planning for the launch of new antimicrobials. They should use these processes along with local horizon scanning processes to plan for local implementation of new antimicrobials.</p> <p>The GDG was aware from the call for evidence that current arrangements for funding new antimicrobials may act as a barrier to their rapid adoption (for example, if new antimicrobials are funded or not funded as part of the tariff arrangements for payment by results [PbR]).</p> <p>The GDG concluded from their experience that these delays are most likely avoidable and that there should be discussion between commissioners and provider organisations early in the approval process if funding concerns for a new antimicrobial are likely to cause delay in its introduction, adoption and diffusion.</p> <p>Laboratory support for prescribing</p> <p>The GDG discussed the role of laboratory support in relation to antimicrobial stewardship and planning for the introduction of a new antimicrobial. The GDG was aware that different laboratories (usually in secondary care setting) report sensitivities to antimicrobials in variable ways. Some trusts only report sensitivity to antimicrobials in their local antimicrobial guidelines whereas others list sensitivity results against antimicrobials that are not recommended for local use.</p> <p>The GDG was aware from the experience of its members that prescribing of antimicrobials may sometimes be inappropriate because a laboratory</p>

sample has been taken and a sensitivity result reported in the absence of other evidence of infection (for example, a wound swab may be taken from an uninfected site and the laboratory may report the sensitivity of commensal organisms to antimicrobials). The GDG agreed that laboratory reporting should reflect national and local treatment guidelines to minimise the likelihood of inappropriate antimicrobials being prescribed for specific conditions. The GDG agreed that prescribers should document the diagnosis and symptoms on the samples submitted to the laboratory to ensure that only pathogenic organisms are treated.

The GDG discussed reporting of antimicrobial sensitivity as an intervention for supporting prescribers to adopt certain antimicrobials. The GDG was aware from the study by McNulty (2011) that the decision to report the sensitivity of an infecting organism to specific antimicrobials will affect whether those antimicrobials are subsequently prescribed.

The GDG members discussed from their experience that the order in which antimicrobial sensitivities are reported also has an effect on prescribing. The GDG was also aware that microorganism sensitivity testing is often incomplete (typically through the use of automated disc dispensers in laboratories) and can omit potentially useful sensitivity findings. Additional tests for these would have resource implications for the laboratory. The discs used generally give sensitivities against 6 antimicrobials.

The GDG agreed that the susceptibilities for which microorganisms are tested, the order in which the antimicrobial sensitivities are reported and whether the results demonstrate a need for antimicrobial treatment are important contributions from clinical microbiology services both to the adoption and diffusion of new medicines and to antimicrobial stewardship.

The GDG concluded that microorganism susceptibility testing and the order of antimicrobial susceptibilities should be in line with:

- national and local treatment guidelines
- the choice of antimicrobial in the local formulary
- the priorities of medicines optimisation and antimicrobial stewardship teams.

Supporting prescribers to implement new antimicrobials

The GDG was aware from their experience that multifaceted interventions to encourage the adoption and diffusion of new antimicrobials among prescribers work better than single interventions. The GDG was aware that evidence from the call for evidence showed a wide variation in approaches to support prescribers to implement new antimicrobials. The GDG concluded that organisations should consider using multiple approaches (based on the examples the GDG considered good practice from the call for evidence) to support the introduction of a new antimicrobial, including:

- electronic alerts to notify prescribers about the antimicrobial
- prescribing guidance about when and where to use the antimicrobial in practice
- issuing new or updated formulary guidelines and antimicrobial prescribing guidelines
- peer advocacy and advice from other prescribers
- providing education or informal teaching on ward rounds
- shared risk management strategies for antimicrobials that are potentially useful but may be associated with adverse events.

	<p>The GDG discussed what information prescribers need to ensure the timely adoption and diffusion of a new antimicrobial by planning for implementation.</p> <p>The GDG concluded that organisations should ensure that all prescribers, including those in urgent care services, community nurses and dentists (as the GDG was aware that these groups are not always made aware of changes promptly) are aware of current local guidelines and are provided with updates if they change.</p> <p>The GDG agreed that organisations should signpost prescribers to the following information about a new antimicrobial:</p> <ul style="list-style-type: none"> • indications and contraindications for use • the spectrum of activity • information on dose selection, including information on bioavailability and tissue penetration (for example, how well does the new antimicrobial penetrate different tissues such as bone, joints or the central nervous system) • dose adjustment for concomitant illness (for example, in renal failure) • duration of course and review dates • the safety and side effects profile • any advantages or disadvantages compared with other antimicrobials • local antimicrobial recommendations, restrictions or criteria for use (including place in therapy, illness severity score) • options for treatment when a patient has an allergy • any other licensing information • any patient monitoring required. <p>The GDG concluded that organisations should indicate where prescribers can find accurate, evidence-based and up-to-date information about a new antimicrobial such as:</p> <ul style="list-style-type: none"> • the electronic medicines compendium • the British National Formulary (BNF) • the British National Formulary for Children (BNFC) • the Medicines and Healthcare products Regulatory Agency (MHRA).
Trade-off between benefits and harms for the monitoring and evaluation of new antimicrobials	<p>The GDG discussed the value and purpose of local monitoring or surveillance following the introduction of a new antimicrobial. The GDG was aware that data on the resistance of microorganisms is now being made available at regional and national level. The English surveillance programme antimicrobial utilisation and resistance (ESPAUR) report (2014) presents antimicrobial use and resistance trends in both primary and secondary care settings. The GDG agreed that this allows organisations to benchmark and compare their data against regional and national data which the GDG recognise as an important aspect of surveillance of a new antimicrobial (see also section 5.6. on antimicrobial resistance surveillance).</p> <p>The GDG agreed that the call for evidence revealed some variation in practice in the processes organisations have in place for monitoring and surveillance for new antimicrobials that have been approved for use (audit, costing audits, reviewing use of non-formulary or new antimicrobials against local or national guidance), to assess if any resistant microorganisms have</p>

developed in the population(s) in which they are being used. This monitoring should also assess the clinical outcomes of therapy (for example, cure and treatment failure rates) with the new antimicrobial and ensure that there is reporting of suspected adverse drug reactions which are not the result of a medication error are collected by the [MHRA](#) through the [Yellow Card Scheme](#).

The GDG concluded that once a new antimicrobial has been approved for local use, organisations should consider ongoing monitoring (based on the examples the GDG considered good practice from the call for evidence) by:

- reviewing whether prescribing is appropriate and in line with the diagnosis and local and national guidelines (antimicrobial use review)
- costing the use of the new antimicrobial
- reviewing the use of non-formulary antimicrobial prescribing
- monitoring and evaluation of local prescribing and resistance patterns.

The GDG discussed how monitoring data should be used and agreed that feedback should be undertaken at an organisational, practice and individual practitioner level; this should include all prescribers who prescribe antimicrobials in any care setting. The GDG agreed that monitoring and reviewing the prescribing data of an individual prescriber and comparing this with that of their peers could be used as part of the individual prescriber's annual self-assessment or personal development plan.

The GDG also discussed and agreed that in keeping with the [NHS Constitution](#) (Department of Health 2014) responsibility for staff to 'raise any genuine concern they may have about a risk' (that is, the risk of increasing antimicrobial resistance), organisations should have an open and transparent culture that allows health professionals to question antimicrobial prescribing practices of colleagues when these are not in line with local and national guidelines and no reason is documented.

The GDG concluded that organisations should develop systems and processes for providing regular updates (at least every year) to individual prescribers and prescribing leads on:

- national and local antimicrobial prescribing patterns
- local antimicrobial resistance patterns
- adverse event patterns (relating to antimicrobial).

The GDG also agreed that organisations should consider providing the information electronically wherever possible.

Supply of antimicrobials

The GDG discussed the barriers to effective antimicrobial stewardship in relation to supplies of antimicrobials that are issued by dentists, out-of-hours services and via other supply routes such as patient group directions. The GDG was aware of the NICE guideline on [patient group directions](#) that recommends that antimicrobials are only included in a patient group direction in specific circumstances (see recommendations 2.1.10 and 2.3.2).

1 **8.6 Recommendations and research recommendations**

2 See section 4.2 for a list of all recommendations and appendix F for a summary of the
3 evidence linking the recommendations.

9 References

- 1
2 Aabenhus R, Jensen JUS, Jorgensen KJ, et al. (2014) biomarkers as point-of-care tests to
3 guide prescription of antibiotics in patients with acute respiratory infections in primary care.
4 Cochrane Database of Systematic Reviews
- 5 Abbo L, Lo K, Sinkowitz-Cochran R, et al. (2013) Antimicrobial Stewardship Programs in
6 Florida's Acute Care Facilities. *Infection Control and Hospital Epidemiology* 34(6):634-37
- 7 Baer G, Baumann P, Buettcher M, et al. (2013) Procalcitonin guidance to reduce antibiotic
8 treatment of lower respiratory tract infection in children and adolescents (ProPAED): A
9 randomised controlled trial. *PloS One* 8(8): e68419
- 10 Bannan A, Buono E, McLaws ML, et al. (2009) A survey of medical staff attitudes to antibiotic
11 approval and stewardship programme. *Internal Medicine Journal* 39:662-68
- 12 Bouadma L, Luyt CE, Tubach F, et al. (2010) Use of procalcitonin to reduce patients'
13 exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised
14 controlled trial. *Lancet* 375(9713): 463-74
- 15 Broom A, Broom J and Kirkby E. (2014) Cultures of resistance? A Bourdieusian analysis of
16 doctors' antibiotic prescribing. *Social Science & Medicine* 110:81-88
- 17 Brust JCM, Litwin AH, Berg KM, et al. (2011) Directly observed antiretroviral therapy in
18 substance abusers receiving methadone maintenance therapy does not cause increased
19 drug resistance. *AIDS Research and Human Retroviruses* 27(5): 535-41
- 20 Butler CC, Simpson SA, Dunstan F, et al. (2012) Effectiveness of multifaceted educational
21 programme to reduce antibiotic dispensing in primary care: practice based randomised
22 controlled trial. *BMJ* 12:344
- 23 Camins BC, King MD, Wells JB, et al. (2009) the impact of an antimicrobial utilisation
24 program on antimicrobial use at a large teaching hospital: a randomised controlled trial.
25 *Infection Control and Hospital Epidemiology* 30(10):931-38
- 26 Capellier G, Mockly H, Charpentier C, et al. (2012) Early-onset ventilator-associated
27 pneumonia in adults randomized clinical trial: comparison of 8 versus 15 days of antibiotic
28 treatment. *PloS One* 7(8): e41290
- 29 Charani E, Castro-Sanchez N, Sevdalis N, et al (2013) Understanding the Determinants of
30 Antimicrobial Prescribing Within Hospitals: The Role of "Prescribing Etiquette" *Clinical
31 Infectious Diseases*. 57:188-96
- 32 Chardin H, Yasukawa K, Nouacer N, et al. (2009) Reduced susceptibility to amoxicillin of oral
33 streptococci following amoxicillin exposure. *Journal of Medical Microbiology* 58(Pt8): 1092-7
- 34 Chastre J, Wolff M, Fagon J, et al. (2003) Comparison of 8 vs 15 days of antibiotic therapy
35 for ventilator-associated pneumonia in adults: a randomized trial. *The Journal of the
36 American Medical Association* 290: 2588-98
- 37
38 Copenhagen study group of urinary tract infections in children (1991) Short-term treatment of
39 acute urinary tract infection in girls. *Scandinavian Journal of Infectious Diseases* 23(2): 213-
40 20
- 41
42 Curran E, Harper P, Loveday H, et al. (2008) Results of a multicentre randomised controlled
43 trial of statistical process control charts and structured diagnostic tools to reduce ward-

- 1 acquired meticillin-resistant *Staphylococcus aureus*: the CHART Project. *The Journal of*
2 *Hospital Infection* 70(2): 127-35
3
- 4 Davey P, Brown E, Charani E, et al. (2013) Interventions to improve antibiotic prescribing
5 practices for hospital inpatients. *The Cochrane Database of Systematic Reviews* 4: Art No.
6 CD003543. DOI: 10.1002/14651858.pub3
7
- 8 Christakis DA, Zimmerman FJ, Wright JA, et al. (2001) A randomised controlled trial of point-
9 of-care evidence to improve the antibiotic prescribing practices for otitis media in children.
10 *Pediatrics* 107(2):e15
- 11 Cortoos P, DeWitte K, Peetermans WE, et al. (2008) Opposing expectations and suboptimal
12 use of a local antibiotic hospital guideline: a qualitative study. *Journal of Antimicrobial*
13 *Chemotherapy* 62:189-95
- 14 De Souza V, MacFarlane A, Murphy AW, et al. (2006) A qualitative study of factors
15 influencing antimicrobial prescribing by non-consultant hospital doctors. *Journal of*
16 *Antimicrobial Chemotherapy* 58:840-43
- 17 Doron S, Nadkarni L, Price LL, et al. (2013) A Nationwide Survey of Antimicrobial
18 Stewardship Practices. *Clinical Therapeutics* 35(6):758-65
- 19 Dranitsaris G, Spizzirri D, Pitre A, et al. (2001) A randomised trial to measure the optimal role
20 of the pharmacist in promoting evidence-based antibiotic use in acute care hospitals.
21 *International Journal of Technology Assessment in Health Care* 17(2):171-80
- 22 Esposito S, Tagliabue C, Picciollo, et al. (2011) procalcitonin measurements for guiding
23 antibiotic treatment in pediatric pneumonia. *Respiratory Medicine* 105:1939-45
- 24 Falagas ME, Bliziotis IA, Rafailidis PI (2007) Do high doses of quinolones decrease the
25 emergence of antibacterial resistance? A systematic review of data from comparative clinical
26 trials. *The Journal of Infection* 55(2): 97-105
27
- 28 Goldman M, Cloud G, Wade K, et al. (2005) A Randomized Study of the Use of Fluconazole
29 in Continuous versus Episodic Therapy in Patients with Advanced HIV Infection and a
30 History of Oropharyngeal Candidiasis: AIDS Clinical Trials Group Study /Mycoses Study
31 Group Study. *Clinical Infectious Diseases* 41: 1473-80
32
- 33 Hasselgren PO, Ivarsson L, Risberg B, et al. (1984) Effects of prophylactic antibiotics in
34 vascular surgery. A prospective, randomized, double-blind study. *Annals of Surgery* 200: 86-
35 92
36
- 37 Hemsell DL, Heard ML, Nobles BJ, et al. (1984) Single-dose cefoxitin prophylaxis for
38 premenopausal women undergoing vaginal hysterectomy. *Obstetrics and Gynecology* 63:
39 285-90
40
- 41 Hemsell DL, Hemsell PG, Heard ML, et al. (1985) Preoperative cefoxitin prophylaxis for
42 elective abdominal hysterectomy. *American Journal of Obstetrics and Gynecology* 63: 225-6
43
- 44 Heyland DK, Dodek P, Muscedere J, et al. (2008) Randomized trial of combination versus
45 monotherapy for the empiric treatment of suspected ventilator-associated pneumonia. *Critical*
46 *Care Medicine* 36: 737-44
47
- 48 Ishibashi K, Kuwabara K, Ishiguro T, et al. (2009) Short-term intravenous antimicrobial
49 prophylaxis in combination with preoperative oral antibiotics on surgical site infection and

- 1 methicillin-resistant *Staphylococcus aureus* infection in elective colon cancer surgery: results
2 of a prospective randomized trial. *Surgery Today* 39: 1032-9
3
- 4 Fine MJ, Stone RA, Lave JR, et al. (2003) Implementation of an evidence-based guideline to
5 reduce duration of intravenous antibiotic therapy and length of stay for patients hospitalized
6 with community-acquired pneumonia: a randomized controlled trial. *American Journal of*
7 *Medicine* 115(5):343-51
- 8 Gerber JS, Prasad PA, Fiks AG, et al. (2013) Effect of an outpatient antimicrobial
9 stewardship intervention on broad-spectrum antibiotic prescribing by primary care
10 paediatricians. *JAMA* 309(22):2345-52
- 11 Gjelstad S, Hoye S, Straand J, et al. (2013) Improving antibiotic prescribing in acute
12 respiratory tract infections: cluster randomised trial from Norwegian general practice
13 (prescription peer academic detailing (Rx-PAD) study). *BMJ* 347:f4403
- 14 Gonzales R, Aagaard EM, Camargo CA, et al. (2011) C-reactive protein testing does not
15 decrease antibiotic use for acute cough illness when compared to a clinical algorithm. *The*
16 *Journal of Emergency Medicine*. 41(1):1-7
- 17 Heritage J, Elliott MN, Stivers T, et al. (2010) Reducing inappropriate antibiotics prescribing:
18 The role of online commentary on physical examination findings. *Patient Education and*
19 *Counseling* 81:119-25
- 20 Hersh AL, Beekmann SE, Polgreen PM, et al. (2009). Antimicrobial stewardship programs in
21 pediatrics. *Infection Control and Hospital* 30(12):1211-17
- 22 Jensen KM, Paladino JA. (1997) Cost effectiveness of abbreviating the duration of
23 intravenous antibacterial therapy with oral fluoroquinolones. *PharmacoEconomics* 11(1):64-
24 74.
- 25 Johannsson B, Beekmann SE, Srinivasan A, et al. (2011) Improving antimicrobial
26 stewardship the evolution of programmatic strategies and barriers. *Epidemiologists of*
27 *America* 32(4):367-74
- 28 Kim JW, Chung J, Choi SH et al. (2012) Early use of imipenem/cilastatin and vancomycin
29 followed by de-escalation versus conventional antimicrobials without de-escalation for
30 patients with hospital-acquired pneumonia in a medical ICU: a randomized clinical trial.
31 *Critical Care* 16: 28
- 32 Kumar S, Little P and Britten N. (2003). Why do general practitioners prescribe antibiotics for
33 sore throat? Grounded theory interview study. *BMJ* 326:1-6
- 34 Leone M, Bechis C, Baumstarck K et al. (2014) De-escalation versus continuation of
35 empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized
36 noninferiority trial. *Intensive Care Medicine* 40: 1399-408
- 37 Lesprit P, Landelle C and Brun-Buisson C. (2012) Clinical impact of unsolicited post-
38 prescription antibiotic review in surgical and medical wards: a randomised controlled trial.
39 *Clinical microbiology and Infection* 19:E91-97
- 40 Linder JA, Schnipper JL, Tsurikova R, et al. (2009) Documentation-based clinical decision
41 support to improve antibiotic prescribing for acute respiratory infections in primary care: a
42 cluster randomised controlled trial. *Informatics in Primary Care* 17:231-40
- 43 Maru DS-R, Kozal MJ, Bruce RD, et al. (2007) Directly administered antiretroviral therapy for
44 HIV-infected drug users does not have an impact on antiretroviral resistance: results from a

- 1 randomized controlled trial. *Journal of Acquired Immune Deficiency Syndromes* (1999) 46:
2 555-63
3
- 4 Manzour S, Bailey B, Girodias J-B, et al. (2010) Impact of procalcitonin on the management
5 of children aged 1 to 36 months presenting with fever without source: a randomised
6 controlled trial. *American Journal of Emergency Medicine* 28:647-53
- 7 McCormick DP, Chonmaitree T, Pittman C, et al. (2005) Non severe acute otitis media: a
8 clinical trial comparing outcomes of watchful waiting versus immediate antibiotic treatment
9 (Structured abstract). *Pediatrics* 115: 1455-65
- 10 McGregor JC, Weekes E, Forrest GN, et al. (2006) Impact of a computerised clinical decision
11 support system on reducing inappropriate antimicrobial use: a randomized controlled trial.
12 *Journal of American Medical Informatics Association* 13:378-84
- 13 McNulty, CAM; Lasseter, GM; Charlett AM, et al. (2011) Does laboratory antibiotic
14 susceptibility reporting influence primary care prescribing in urinary tract infection and other
15 infections? *Journal Antimicrobial Chemotherapy* 66: 1396–1404
- 16 Moltzahn F, Haeni K, Birkhauser FD, et al. (2013) Peri-interventional antibiotic prophylaxis
17 only vs continuous low-dose antibiotic treatment in patients with JJ stents: A prospective
18 randomised trial analysing the effect on urinary tract infections and stent-related symptoms.
19 *BJU International* 111: 289-95
- 20 Mountokalakis T, Skounakis M, Tselentis J. (1985) Short-term versus prolonged systemic
21 antibiotic prophylaxis in patients treated with indwelling catheters. *Journal of Urology* 134:
22 506-8
- 23 Micek ST. (2014) A randomized controlled trial of an antibiotic discontinuation policy for
24 clinically suspected ventilator-associated pneumonia. *Chest* 125: 1791-9
- 25 Oosterheert JJ, Bonten MJM, Schneider MME, et al (2006) Effectiveness of early switch from
26 intravenous to oral antibiotics in severe community acquired pneumonia: multicentre
27 randomised trial. *British Medical Journal*
- 28 Palmer LB, Smaldone GC. (2014) Reduction of bacterial resistance with inhaled antibiotics in
29 the intensive care unit. *American Journal of Respiratory and Critical Care Medicine* 189:
30 1225-33
- 31 Palmer LB, Smaldone GC, Chen JJ, et al. (2008) Aerosolized antibiotics and ventilator-
32 associated tracheobronchitis in the intensive care unit. *Critical Care Medicine* 36: 2008-13
- 33 Revankar WR, Kirkpatrick M, Robert K, et al. (1998) A randomized trial of continuous or
34 intermittent therapy with fluconazole for oropharyngeal candidiasis in HIV-infected patients:
35 clinical outcomes and development of fluconazole resistance. *American Journal of Medicine*
36 105: 7-11
- 37 Stahl GE, Topf P, Fleisher GR, et al. (1984) Single-dose treatment of uncomplicated urinary
38 tract infections in children. *Annals of Emergency Medicine* 13: 705-8
- 39 Schouten JA, Hulscher MEJL, Natsch S, et al. (2007). Barriers to optimal antibiotic use for
40 community-acquired pneumonia at hospitals: a qualitative study. *Quality & Safety in Health
41 Care*, 16(2):143-49
- 42 Scheetz MH, Bolon MK, Postelnick M, et al (2009) Cost-effectiveness analysis of an
43 antimicrobial stewardship team on bloodstream infections: a probabilistic analysis. *Journal of
44 Antimicrobial Chemotherapy* 63: 816–825

- 1 Schuetz P, Muller B, Christ-Cain M, et al. (2013) Procalcitonin to initiate or discontinue
2 antibiotics in acute respiratory tract infections. *Evidence-Based Child Health* 8(4):1297-1371
- 3 Seager JM, Howell-Jones RS, Dunstan FD, et al. (2006) A randomised controlled trial of
4 clinical outreach education to rationalise antibiotic prescribing for acute dental pain in the
5 primary care setting. *British Dental Journal* 201(4):217-22
- 6 Shojania KG, Yokoe D, Platt R, et al. (1998) Reducing vancomycin use utilizing a computer
7 guideline: results of a randomized controlled trial. *Journal of American Medical Informatics
8 Association* 5:554-62
- 9 Simpson SA, Wood F and Butler CC. (2007). General practitioners' perceptions of
10 antimicrobial resistance: a qualitative study. *The Journal of Antimicrobial Chemotherapy*,
11 59(2):292-96
- 12 Singh N, Rogers P, Atwood CW, et al. (2000) Short-course empiric antibiotic therapy for
13 patients with pulmonary infiltrates in the intensive care unit. A proposed solution for
14 indiscriminate antibiotic prescription. *American Journal of Respiratory and Critical Care
15 Medicine* 162: 505-11
- 16 Solomon DH, van Houten L, Glynn RJ, et al. (2001) Academic detailing to improve use of a
17 broad-spectrum antibiotics at an academic medical center. *Archives of Internal Medicine*
18 161:1897-1902
- 19 Spurling GKP, Del Mar CB, Dooley L, et al. (2013) Delayed antibiotics for respiratory
20 infections. *Cochrane Database of Systematic Reviews*
- 21 Teo CK, Baysari MT and Day RO. (2013) Understanding compliance to an antibiotic
22 prescribing policy: Perspectives of policymakers and prescribers. *Journal of Pharmacy
23 Practice and Research* 43(1):32-36
- 24 van Zanten ARH, Oudijk M, Nohlmans-Paulssen MKE, et al. (2007) Continuous vs.
25 intermittent cefotaxime administration in patients with chronic obstructive pulmonary disease
26 and respiratory tract infections: pharmacokinetics/pharmacodynamics, bacterial susceptibility
27 and clinical efficacy. *British Journal of Clinical Pharmacology* 63: 100-9
- 28 Wall E, Verkooyen RP, Mintjes-de GJ, et al. (1992) Prophylactic ciprofloxacin for catheter-
29 associated urinary-tract infection. *Lancet* 339: 946-51
- 30 Wigton RS, Darr CA, Corbett KK, et al. (2008) How do community practitioners decide
31 whether to prescribe antibiotics for acute respiratory tract infections? *Journal of General
32 Internal Medicine* 23(10):1615-20
- 33 Wood F, Simpson S and Butler CC. (2007) Socially responsible antibiotic choices in primary
34 care: a qualitative study of GPs' decisions to prescribe broad-spectrum and fluoroquinolone
35 antibiotics. *Family Practice* 24(5):427-34

10 Glossary

2 This glossary provides brief definitions and explanations of terms used within this guideline.
3 Further definitions and explanation of terms can be found on the NICE glossary page.

4 **Acute otitis media (AOM)**

5 An acute inflammation of the middle ear

6 **Bacterial isolate**

7 The separation of mixed bacterial strains in to single strains for identification

8 **Febrile morbidity**

9 Any infectious complication following surgery

10 **In vitro**

11 An event taking place in a test tube, culture dish, or elsewhere outside a living organism

12 **Prophylaxis**

13 Treatment given or action taken to prevent infection

14 **Spectrum**

15 The range of organisms against which an antimicrobial has an effective action

16 **Superinfection**

17 An infection that happens following or in addition to an earlier infection

18 **Surveillance**

19 Surveillance of antimicrobial resistance is the tracking of changes in microbial populations

20 **Ventilator associated pneumonia**

21 A pneumonia occurring in a patient within 48 hours or more after intubation (insertion of a
22 breathing tube, via the mouth or through a tracheostomy, into the airway) which was not
23 present before

24

25

26