NICE Medicines and Prescribing Centre

Antimicrobial stewardship

Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use

Full guideline

Methods, evidence and recommendations

August 2015

National Institute for Health and Care Excellence

Update information

Minor changes since publication

January 2018: Some links to other guidelines and external sources of information were updated.

These changes can be seen in the short version of the guideline at http://www.nice.org.uk/guidance/NG15

In this version of the guideline, please note that since original publication the Health and Social Care Information Centre has been replaced by NHS Digital (http://digital.nhs.uk)

Disclaimer

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Acknowledgements

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

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 is it hoped that the future effectiveness of antimicrobials can be preserved.

Antimicrobial resistance – background

In 2014 Public Health England 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 World Health Organization Antimicrobial resistance: global report on surveillance (2014) states that 'AMR develops when a microorganism (bacteria, fungus, virus or parasite) no longer responds to a drug to which it was originally sensitive. This means that standard treatments no longer work; infections are harder or impossible to control; the risk of the spread of infection to others is increased; illness and hospital stays are prolonged, with added economic and social costs; and the risk of death is greater—in some cases, twice that of patients who have infections caused by non-resistant bacteria.'

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

In 2013, the Department of Health published the UK five year antimicrobial resistance strategy 2013 to 2018, 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, to:

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

An antimicrobial resistance strategy impact assessment published to accompany the 5-year strategy aimed to support the introduction of the strategy and highlighted the importance of preserving current effective therapies by 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 antimicrobial resistance strategy, more information is provided in the government's antimicrobial resistance collection.

In 2014 the HM Government publication The UK 5 Year Antimicrobial Resistance (AMR) Strategy 2013–2018 Annual progress report and implementation plan set out the ambition to 'reduce overall antibiotic prescribing, encourage narrow spectrum prescribing, improve the diversity of the antibiotics prescribed and establish new primary and secondary care antibiotic prescribing quality measures to minimise the development of resistance to commonly used antibiotics'.

Resources for organisations and health professionals

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

In 2011 the Department of Health Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI) published Antimicrobial stewardship: Start smart - then focus (updated in 2015) which provides guidance for antimicrobial stewardship in hospitals in England. The guidance stresses the importance of clear governance arrangements when managing antimicrobial resistance.

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

In 2013 the Department of Health and Public Health England published antimicrobial prescribing and stewardship competencies, which aim to improve the quality of antimicrobial treatment and stewardship, and so reduce the risks and ill-effects of inadequate and inappropriate treatment.

Public Health England has also published guidance on:

- Primary care guidance: diagnosing and managing infections (2013)

- Managing common infections: guidance for consultation and adaptation (2010, last updated 2015)
- Carbapenemase-producing Enterobacteriaceae: early detection, management and control toolkit for acute trusts (2014).

National prescribing data

Antimicrobial prescribing data are available through the Health and Social Care Information Centre (HSCIC). The data report monthly GP practice prescribing and provide annual reports on prescribing by dentists. The NHS Business Services Authority (NHS BSA) processes all prescriptions dispensed in England in the community setting and collates prescribing data, which can be analysed down to individual prescriber level. Furthermore, the Department for Environment, Food and Rural Affairs (DEFRA) is reviewing antibiotic use in both humans and animals as part of UK AMR strategy: measuring success.

1.2 Legal framework

1.2.1 Regulatory requirements

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

In the Fundamental standards the CQC sets out what providers should do to comply with The Health and Social Care Act 2008 (Regulated Activities) Regulations 2014. The CQC set out the requirements for Regulation 12 and Regulation 15 of The Health and Social Care Act 2008 (Regulated Activities) Regulations 2014 which cover infection control and cleanliness.

Guidance for providers on compliance with Regulation 12 is issued by the Department of Health in The Health and Social Care Act 2008: Code of Practice on the prevention and control of infections and related guidance (2010, updated 2015). The 'Code of Practice' sets out '10 criteria against which a registered provider will be judged on how it complies with the registration requirement for cleanliness and infection control' (Department of Health 2010). In 'part 3: guidance for compliance', criterion 9 outlines the processes that should be in place to ensure prudent prescribing and antimicrobial stewardship. It suggests that there should be an ongoing programme of audit, revision and update. In healthcare this is usually monitored by an antimicrobial management team or local prescribing advisors.

Children's care homes

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

1.3 Definitions used in the guideline

Antimicrobial stewardship

The term 'antimicrobial stewardship' is defined in the annual report of the Chief Medical Officer, volume two, 2011: Infections and the rise of antimicrobial resistance as an approach

that ‘embodies an organisational or healthcare-system-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness’.

Antimicrobial resistance

The term ‘antimicrobial resistance’ is defined according to the Executive Board of the World Health Organization (WHO) as the ‘loss of effectiveness of any anti-infective medicine, including antiviral, antifungal, antibacterial and antiparasitic medicines’.

Antimicrobial or antimicrobial medicine

The term ‘antimicrobials’ and ‘antimicrobial medicines’ includes all anti-infective therapies (antiviral, antifungal, antibacterial and antiparasitic medicines), and all formulations (oral, parenteral and topical agents).

Organisations

The term 'organisations' (also known as the ‘service’) is used to include all commissioners and providers, unless specified otherwise in the text.

Commissioners are those individuals who undertake commissioning which is 'the process used by health services and local authorities to: identify the need for local services; assess this need against the services and resources available from public, private and voluntary organisations; decide priorities; and set up contracts and service agreements to buy services. As part of the commissioning process, services are regularly evaluated'.

Providers are organisations that directly provide health or social care services to people (such as social enterprises, dentists, GPs, pharmacies, out-of-hours services, hospitals).

Health and social care practitioners

The term 'health and social care practitioners' is used to define the wider care team, including but not limited to, case managers, care coordinators, GPs, hospital doctors, microbiologists, pharmacists, nurses and social workers.

Local decision-making groups

Local decision-making groups include area prescribing committees, drug and therapeutics committees, commissioner-based prioritisation groups, and clinical networks that are responsible for making decisions on behalf of a local health and/or social care organisation.

Other definitions used in this guideline are given in the glossary.

1.4 Person-centred care

This guideline offers best practice advice on the effective use of antimicrobial medicines.

Patients and health professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their health professionals. If the person is under 16, their family or carers should also be given information and support to help the child or young person to make decisions about their treatment. Health professionals should follow the Department of Health’s advice on consent. If a person does not have capacity to make decisions, health and social care

practitioners should follow the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards.

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

1.5 Strength of recommendations

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

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

1.5.1 Interventions that must (or must not) be used

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

1.5.2 Interventions that should (or should not) be used – a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the majority of people, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that an intervention will not be of benefit for most people.

1.5.3 Interventions that could be used

We use 'consider' when we are confident that an intervention will do more good than harm for most people, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the health professional should spend more time considering and discussing the options with the person.

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
- NICE prepares the scope (stakeholders can comment on the draft at a scoping workshop and through a 4-week consultation)
- 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 guideline is revised in line with comments received from stakeholders during consultation
- the final guideline is published.

NICE produces a number of different versions of this guideline:

- ‘full guideline’ contains all the recommendations, plus details of the methods used and the underpinning evidence
- ‘short version’ 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 guideline. The other versions can be downloaded from NICE at www.nice.org.uk.

2.2 Remit

NICE received the remit for the guideline from the Department of Health and Public Health England.

2.3 Who developed the guideline

A multidisciplinary Guideline Development Group (GDG) comprising health professionals and lay members developed this guideline (see The Guideline Development Group, NICE project team and NICE quality assurance team for more information) with support from the Medicines and Prescribing Centre at NICE.

The GDG was convened by the Medicines and Prescribing Centre and was chaired by Professor Alastair Hay, in accordance with guidance from NICE.

The group met regularly during the development of the guideline. At the start of the guideline development process, all GDG members declared interests in line with the NICE code of practice on declaring and dealing with conflicts of interest, this included any consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest. The 2007 conflicts of interest policy was followed until September 2014, when an updated policy was published.

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

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

2.4 Purpose and audience

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

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

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

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

2.5 What this guideline covers

The guideline covers:

- Health and social care practitioners (a term used to define the wider care team of hospital staff [including microbiologists and infection control staff], community matrons and case managers, GPs, dentists, podiatrists, pharmacists and community nurses [including those staff working in out-of-hours services], domiciliary care workers and care home staff [registered nurses and social care practitioners working in care homes], social workers and case managers).
- Organisations commissioning (for example, clinical commissioning groups or local authorities), providing or supporting the provision of care (for example, national or professional bodies, directors of public health, health and wellbeing boards, healthcare trusts and locum agencies).
- Adults, young people and children (including neonates) using antimicrobials, or those caring for these groups.

Settings covered include:

- All publicly funded health and social care commissioned or provided by NHS organisations, local authorities (in England), independent organisations or independent contractors.

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

For further details please refer to the scope in appendix B and review questions in appendix C.2.

2.6 What this guideline does not cover

The guideline does not cover:

- specific clinical conditions (although some evidence identified included patients with a specific infection such as community acquired pneumonia)
- named medicines
- public health awareness of antimicrobial resistance
- research into new antimicrobials
- immunisation and vaccination
- antimicrobial household cleaning products
- antimicrobial use in animals
- hand hygiene, decolonisation and infection prevention and control measures
- medicines adherence, except where there are specific issues for health and social care practitioners to address relating to antimicrobials
- access to medicines, including local decision-making for medicines not included on local formularies
- medicines shortages, including supply issues and discontinued medicines
- prescription charges
- waste medicines.

2.7 Related NICE guidance

2.7.1 Published

- Medicines optimisation. NICE guideline NG5 (2015).

- Pneumonia. NICE guideline CG191 (2014).
- Drug allergy. NICE guideline CG183 (2014).
- Managing medicines in care homes. NICE guideline SC1 (2014).
- Patient group directions. NICE guideline MPG2 (2013).
- Infection. NICE guideline CG139 (2012).
- Patient experience in adult NHS services. NICE guideline CG138 (2012).
- Developing and updating local formularies. NICE guideline MPG1 (2012).
- Service user experience in adult mental health. NICE guideline CG136 (2011).
- Prevention and control of healthcare-associated infections NICE guideline PH36 (2011).
- Medicines adherence. NICE guideline CG76 (2009).
- Surgical site infection. NICE guideline CG74 (2008).
- Respiratory tract infections – antibiotic prescribing NICE guideline CG69 (2008).

2.7.2 Under development

NICE is currently developing the following related guidance (details available from the NICE website):

- Antimicrobial stewardship: changing risk-related behaviours in the general population. NICE guideline. Publication 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 4.1). 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.

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 NHS?

3.1.2 Writing the review protocols

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

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

Each review protocol includes:

- the review question
- objectives
- type of review
- language
- study design
- status
- population
- intervention
- comparator
- outcomes
- other criteria for inclusion/exclusion of studies
- search strategies
- review strategies
- identified papers from the scoping search for background, including relevant legislation (UK) or national policy
- identified papers from the scoping search that address the review question.

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

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

3.2 Searching for evidence

3.2.1 Clinical and health economic literature searching

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

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

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

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

3.3 Reviewing the evidence

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

3.3.1 Inclusion and exclusion criteria

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

3.3.2 Methods of combining clinical studies

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

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

3.3.3 Types of studies

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

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

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

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

3.3.4 Call for evidence

Following the review of the published literature, the NICE project team (in consultation with the GDG) considered that there was insufficient published evidence for the review question relating to the timely adoption and diffusion of a new antimicrobial. Therefore a call for evidence was undertaken in line with section 8 of the Interim methods guide for developing good practice guidance. An email, with questions agreed by the GDG, was sent to all those who had registered for news and updates from the Medicines and Prescribing Centre and all stakeholders registered for this guideline.

3.3.5 Appraising the quality of evidence by outcomes

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

The evidence for each outcome was examined separately for the quality elements listed and defined in table 2. Each element was graded using the quality levels listed in table 3. The main criteria considered in the rating of these elements are discussed below. Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall quality assessment for each outcome (table 4).

Table 2: Description of the elements in GRADE used to assess the quality of 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

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

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

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

3.3.6 Evidence statements (summarising and presenting results for effectiveness)

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

3.4 Evidence of cost effectiveness

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

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

3.5 Developing recommendations

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

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

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

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

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

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

See section 9 of Developing NICE guidelines: the manual (2014) for more information on developing and wording recommendations.

3.6 Research recommendations

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

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

3.7 Validation review

3.7.1 Validation process

This guideline was subject to a 4-week public consultation. This allowed stakeholders, members of the public and other NICE teams to peer review the document as part of the quality assurance process. All comments received from registered stakeholders within the specified deadline were responded to. All comments received and responses given are posted on the NICE website.

3.7.2 Updating the guideline

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

3.7.3 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.

3.7.4 Funding

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

4 Guideline summary

4.1 Full list of recommendations

All antimicrobials

Recommendations for organisations (commissioners and providers)

Antimicrobial stewardship programmes

1. **Commissioners should ensure that antimicrobial stewardship operates across all care settings as part of an antimicrobial stewardship programme.**

2. **Establish an antimicrobial stewardship programme, taking account of the resources needed to support antimicrobial stewardship across all care settings.**

3. **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 individual 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 antimicrobial use, including hospital admissions for potentially avoidable life-threatening infections, infections with *Clostridium difficile* or adverse drug reactions such as anaphylaxis
    - providing education and training to health and social care practitioners about antimicrobial stewardship and antimicrobial resistance
    - integrating audit into existing quality improvement programmes.

4. **Ensure that roles, responsibilities and accountabilities are clearly defined within an antimicrobial stewardship programme.**

5. **Involve lead health and social care practitioners in establishing processes for developing, reviewing, updating and implementing local antimicrobial guidelines in line with national guidance and informed by local prescribing data and resistance patterns.**

6. **Consider developing systems and processes for providing regular updates (at least every year) to individual prescribers and prescribing leads on:**
    - individual prescribing benchmarked against local and national antimicrobial prescribing rates and trends
    - local and national antimicrobial resistance rates and trends

- patient safety incidents related to antimicrobial use, including hospital admissions for potentially avoidable life-threatening infections, infections with *C. difficile* or adverse drug reactions such as anaphylaxis.

7. Consider developing systems and processes for identifying and reviewing whether hospital admissions are linked to previous prescribing decisions in patients with potentially avoidable infections (for example, *Escherichia coli* bacteraemias, mastoiditis, pyelonephritis, empyema, quinsy or brain abscess).

Antimicrobial stewardship teams

8. Organisations establishing antimicrobial stewardship teams should ensure that the team has core members (including an antimicrobial pharmacist and a medical microbiologist) and can co-opt additional members depending on the care setting and the antimicrobial issue being considered.

9. Support antimicrobial stewardship teams, by developing processes that promote antimicrobial stewardship or by allocating resources, to:

- review prescribing and resistance data and identify ways of feeding this information back to prescribers in all care settings
- promote education for prescribers in all care settings
- assist the local formulary decision-making group with recommendations about new antimicrobials
- update local formulary and prescribing guidance
- work with prescribers to explore the reasons for very high, increasing or very low volumes of antimicrobial prescribing, or use of antimicrobials not recommended in local (where available) or national guidelines
- provide feedback and advice to prescribers who prescribe antimicrobials outside of local guidelines when it is not justified.

Antimicrobial stewardship interventions

10. Consider using the following antimicrobial stewardship interventions:

- review of prescribing by antimicrobial stewardship teams to explore the reasons for increasing, very high or very low volumes of antimicrobial prescribing, or use of antimicrobials not recommended in local (where available) or national guidelines
- promotion of antimicrobials recommended in local (where available) or national guidelines
- IT or decision support systems
- education-based programmes for health and social care practitioners, (for example, academic detailing, clinical education or educational outreach).

11. Consider providing IT or decision support systems that prescribers can use to decide:

- whether to prescribe an antimicrobial or not, particularly when antimicrobials are frequently prescribed for a condition but may not be the best option

- whether alternatives to immediate antimicrobial prescribing may be appropriate (for example, back-up [delayed] prescribing or early review if concerns arise).

12. **Consider developing systems and processes to ensure that the following information is provided when a patient's care is transferred to another care setting:**
    - information about current or recent antimicrobial use
    - information about when a current antimicrobial course should be reviewed
    - information about who a patient should contact, and when, if they have concerns about infection.

13. **Consider prioritising the monitoring of antimicrobial resistance, to support antimicrobial stewardship across all care settings, taking into account the resources and programmes needed.**

14. **Consider supplying antimicrobials in pack sizes that correspond to local (where available) and national guidelines on course lengths.**

15. **Consider evaluating the effectiveness of antimicrobial stewardship interventions by reviewing rates and trends of antimicrobial prescribing and resistance.**

Communication

16. **Encourage and support prescribers only to prescribe antimicrobials when this is clinically appropriate.**

17. **Encourage health and social care practitioners across all care settings to work together to support antimicrobial stewardship by:**
    - communicating and sharing consistent messages about antimicrobial use
    - sharing learning and experiences about antimicrobial resistance and stewardship
    - referring appropriately between services without raising expectations that antimicrobials will subsequently be prescribed.

18. **Consider developing local networks across all care settings to communicate information and share learning on:**
    - antimicrobial prescribing
    - antimicrobial resistance
    - patient safety incidents.

19. **Consider developing local systems and processes for peer review of prescribing. Encourage an open and transparent culture that allows health professionals to question antimicrobial prescribing practices of colleagues when these are not in line with local (where available) or national guidelines and no reason is documented.**

20. **Encourage senior health professionals to promote antimicrobial stewardship within their teams, recognising the influence that senior prescribers can have on prescribing practices of colleagues.**

21. **Raise awareness of current local guidelines on antimicrobial prescribing among all prescribers, providing updates if the guidelines change.**

Laboratory testing

22. **Ensure that laboratory testing and the order in which the susceptibility of organisms to antimicrobials is reported is in line with:**
    - national and local treatment guidelines
    - the choice of antimicrobial in the local formulary
    - the priorities of medicines management and antimicrobial stewardship teams.

Recommendations for prescribers and other health and social care practitioners

Antimicrobial guidelines

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

Recommendations for prescribers

Antimicrobial prescribing

24. **When prescribing antimicrobials, prescribers should follow local (where available) or national guidelines on:**
    - prescribing the shortest effective course
    - the most appropriate dose
    - route of administration.

25. **When deciding whether or not to prescribe an antimicrobial, take into account the risk of antimicrobial resistance for individual patients and the population as a whole.**

26. **When prescribing any antimicrobial, undertake a clinical assessment and document the clinical diagnosis (including symptoms) in the patient's record and clinical management plan.**

27. **For patients in hospital who have suspected infections, take microbiological samples before prescribing an antimicrobial and review the prescription when the results are available.**

28. **For patients in primary care who have recurrent or persistent infections, consider taking microbiological samples when prescribing an antimicrobial and review the prescription when the results are available.**

29. **For patients who have non-severe infections, consider taking microbiological samples before making a decision about prescribing an antimicrobial, providing it is safe to withhold treatment until the results are available.**

30. **Consider point-of-care testing in primary care for patients with suspected lower respiratory tract infections, as described in the NICE guideline on pneumonia.**

31. **Prescribers should take time to discuss with the patient and/or their family members or carers (as appropriate):**
    - the likely nature of the condition
    - why prescribing an antimicrobial may not be the best option
    - alternative options to prescribing an antimicrobial
    - their views on antimicrobials, taking into account their priorities or concerns for their current illness and whether they want or expect an antimicrobial
    - the benefits and harms of immediate antimicrobial prescribing
    - what they should do if their condition deteriorates (safety netting advice) or they have problems as a result of treatment
    - whether they need any written information about their medicines and any possible outcomes.

32. **When an antimicrobial is a treatment option, document in the patient's records (electronically wherever possible):**
    - 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), including the planned duration of any treatment.

33. **Do not issue an immediate prescription for an antimicrobial to a patient who is likely to have a self-limiting condition.**

34. **If immediate antimicrobial prescribing is not the most appropriate option, discuss with the patient and/or their family members or carers (as appropriate) other options such as:**
    - self-care with over-the-counter preparations
    - back-up (delayed) prescribing
    - other non-pharmacological interventions, for example, draining the site of infection.

35. **When a decision to prescribe an antimicrobial has been made, take into account the benefits and harms for an individual patient associated with the particular antimicrobial, including:**
    - possible interactions with other medicines or any food and drink
    - 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)
    - the risk of selection for organisms causing healthcare-associated infections, for example, *C. difficile*.

36. **When prescribing is outside local (where available) or national guidelines, document in the patient's records the reasons for the decision.**

37. **Do not issue repeat prescriptions for antimicrobials unless needed for a particular clinical condition or indication. Avoid issuing repeat prescriptions for longer than 6 months without review and ensure adequate monitoring for individual patients to reduce adverse drug reactions and to check whether continuing an antimicrobial is really needed.**

Prescribing intravenous antimicrobials

38. **Use an intravenous antimicrobial from the agreed local formulary and in line with local (where available) or national guidelines for a patient who needs an empirical intravenous antimicrobial for a suspected infection but has no confirmed diagnosis.**

39. **Consider reviewing intravenous antimicrobial prescriptions at 48–72 hours in all health and care settings (including community and outpatient services). Include response to treatment and microbiological results in any review, to determine if the antimicrobial needs to be continued and, if so, whether it can be switched to an oral antimicrobial.**

New antimicrobials

Recommendations for organisations (commissioners and providers)

40. **Consider establishing processes for reviewing national horizon scanning to plan for the release of new antimicrobials.**

41. **Consider using 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 include representatives from different care settings and other local organisations to minimise the time to approval.**

42. **Consider using multiple approaches 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 patient safety incidents.

43. **Once a new antimicrobial has been approved for local use, organisations should consider ongoing monitoring by:**
    - conducting an antimicrobial use review (reviewing whether prescribing is appropriate and in line with the diagnosis and local [where available] and national guidelines)
    - costing the use of the new antimicrobial
    - reviewing the use of non-formulary antimicrobial prescribing
    - evaluating local prescribing and resistance patterns
    - reviewing clinical outcomes such as response to treatment, treatment rates, emerging safety issues, tolerability and length of hospital stay.

Recommendations for local decision-making groups

44. **Consider co-opting members with appropriate expertise in antimicrobial stewardship when considering whether to approve the introduction of a new antimicrobial locally; this may include those involved in the antimicrobial stewardship team (see also recommendation 8).**

45. **Ensure that local formularies, prescribing guidelines and care pathways are updated when new antimicrobials are approved for use.**

46. **When evaluating a new antimicrobial for local use and for inclusion in the local formulary, take into account:**
    - the need for the new antimicrobial
    - its clinical effectiveness
    - 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 rates and trends 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 plans for introducing the new antimicrobial.

47. **Local decision-making groups should assess the benefits and risks of restricting access to a new antimicrobial.**

48. **If access to a new antimicrobial is restricted:**
    - document the rationale for and the nature of the restriction, and ensure that this information is publicly available
    - review the restriction regularly to determine that it is still appropriate.

49. **Ensure that there is a plan for the timely introduction, adoption and diffusion of a new antimicrobial when this has been recommended for use.**

50. **Discuss with commissioners early in the approval process if funding concerns for a new antimicrobial are likely to cause delay in its introduction, adoption and diffusion.**

51. **Indicate where prescribers can find accurate, evidence-based and up-to-date information about the new antimicrobial, such as the:**
    - British National Formulary (BNF)
    - British National Formulary for Children (BNFC)
    - electronic Medicines Compendium (eMC)
    - European Medicines Agency (EMA)
    - Medicines and Healthcare products Regulatory Agency (MHRA).

4.1.1 Research recommendations

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

4.2 Who should take action

This guideline is for: commissioners, providers and health and social care practitioners involved with using antimicrobial medicines as part of their remit, working within the NHS; it may also be of interest to local authorities and the wider public, private, voluntary and community sector organisations.

In addition, it may also be of interest to people who use antimicrobial medicines as part of managing their healthcare, their families and carers and other members of the public.

For the purpose of this guideline, when the term ‘organisations’ is used, this includes all commissioners and providers, unless specified otherwise in the text. Commissioners are those individuals who undertake commissioning, which is ‘the process used by health services and local authorities to: identify the need for local services; assess this need against the services and resources available from public, private and voluntary organisations; decide priorities; and set up contracts and service agreements to buy services. As part of the commissioning process, services are regularly evaluated’. Providers are organisations that directly provide health or social care services.

Table 5: Who should take action?

Who should take action?	Recommendations
Commissioners (this may include clinical commissioning groups, commissioners and senior managers in local authorities)	Recommendation 1

Who should take action?	Recommendations
Organisations (this may include, but is not limited to clinical commissioning groups, commissioners and senior managers in local authorities and the NHS providers of health and social care services or other service)	Recommendations 2 - 22 Recommendations 40 - 43
Local decision-making groups	Recommendations 44 - 51
All prescribers	Recommendations 24 - 39
All health and social care practitioners	Recommendation 23

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 2015) guidance was published 'to provide an outline of evidence-based antimicrobial stewardship in the secondary healthcare setting'.

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

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

5.2 Review question

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

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

5.3 Evidence review

5.3.1 Clinical evidence

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

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

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

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

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

The Cochrane review found that interventions to change antibiotic prescribing were associated with a decrease in *Clostridium difficile*-resistant Gram negative bacteria, meticillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE). However, the authors found only 6 interventions (29%) with reliable data on a change in antibiotic prescribing. This was reported as a major confounder in the evidence base

because (the authors report) there are not enough data to estimate the likely impact of change in prescribing on microbial outcomes.

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

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

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

Table 6: Summary of included studies for the review question on reducing antimicrobial resistance

Study	Population	Intervention(s)	Comparison	Key critical outcomes
Bouadma (2010) *France*	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.	• Emergence of organisms resistant to antimicrobials • Clinical outcomes • Unintended consequences • Hospitalisation and health and social care utilisation
Brust (2011) *USA*	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).	• Emergence of organisms resistant to antimicrobials • Clinical outcomes • Patient adherence
Capellier (2012) *France*	Adults mechanically ventilated for more than 24 hours and less than 8 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.	• Emergence of organisms resistant to antimicrobials • Clinical outcomes • Unintended consequences • Hospitalisation and health and social care utilisation
Chardin (2009) *France*	Adults undergoing tooth extraction eligible for antibiotic prophylaxis.	Study of dental infection prophylaxis. Three days of amoxicillin (1 g twice daily by mouth) and placebo for 4 days.	Seven days of amoxicillin (dose not described).	• Emergence of organisms resistant to antimicrobials • Clinical outcomes
Chastre (2003) *France*	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.	• 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.		• Unintended consequences • Hospitalisation and health and social care utilisation
Copenhagen study group of urinary tract infections in children (1991) *Denmark*	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.	• Emergence of organisms resistant to antimicrobials • Clinical outcomes • Unintended consequences
Curran (2008) *UK*	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.	• Emergence of organisms resistant to antimicrobials
Davey (2013) *UK*	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.	• Emergence of organisms resistant to antimicrobials
Falagas (2007) *Greece*	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 2 treatment groups (1 receiving a higher dose of quinolones than the other) and for at least 1 patient the causative organism persisted during or after treatment.	Lower dose of quinolone than the intervention arm.	• Emergence of organisms resistant to antimicrobials • Clinical outcomes • Unintended consequences
Goldman (2005) *USA*	Adults with HIV infection.	Study of prophylaxis in community setting.	Fluconazole administered only for oropharyngeal	• Emergence of organisms resistant to antimicrobials

Study	Population	Intervention(s)	Comparison	Key critical outcomes
		200 mg of fluconazole orally 3 times weekly on a continuous basis.	candidiasis or oesophageal candidiasis episodes.	• Clinical outcomes
Hasselgren (1984) *Sweden*	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 of therapy with cefuroxime, or 3 days of therapy with cefuroxime.	Placebo control group.	• Emergence of organisms resistant to antimicrobials • Clinical outcomes • Unintended consequences
Hemsell (1985) *USA*	Women undergoing elective abdominal hysterectomy.	Study of prophylaxis in surgery. One single 2 g dose of cefoxitin. Two single 2 g doses of cefoxitin. Three single 2 g doses of cefoxitin, all with placebo blinding.	Between intervention arms.	• Emergence of organisms resistant to antimicrobials • Clinical outcomes • Hospitalisation and health and social care utilisation
Hemsell (1984) *USA*	Premenopausal women scheduled for abdominal hysterectomy.	Study of prophylaxis in surgery. One 2 g dose of cefoxitin and 2 placebo doses.	Three 2 g doses of cefoxitin.	• Emergence of organisms resistant to antimicrobials • Clinical outcomes • Unintended consequences • Hospitalisation and health and social care utilisation
Heyland (2008) *Canada*	Critically ill adult patients mechanically ventilated for ≥96 hours who developed suspected pneumonia while intubated and ventilated.	Study of treatment for ventilator associated pneumonia. Initial unblinded therapy with meropenem (1 g every 8 hours) and ciprofloxacin (400 mg every 12 hours).	Initial unblinded therapy with meropenem (1 g every 8 hours) alone.	• Emergence of organisms resistant to antimicrobials • Clinical outcomes • Unintended consequences • Hospitalisation and health and social care utilisation
Ishibashi (2009) *Japan*	Adults undergoing elective surgery for colon cancer.	Study of prophylaxis in surgery. A single dose of IV antibiotics postoperatively 1 hour post-surgery.	Four additional doses of IV antibiotics for 2 consecutive days.	• Emergence of organisms resistant to antimicrobials • Clinical outcomes
Lesprit (2013) *France*	Adults in surgical and medical wards.	Post-antibiotic prescription review by an infectious diseases physician with	Usual care by ward physician only.	• Emergence of organisms resistant to antimicrobials

Study	Population	Intervention(s)	Comparison	Key critical outcomes
		a recommendation to the prescriber.		• Clinical outcomes • Hospitalisation and health and social care utilisation
Maru (2007) *USA*	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.	• Emergence of organisms resistant to antimicrobials • Clinical outcomes
McCormick (2005) *USA*	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.	• Emergence of organisms resistant to antimicrobials • Clinical outcomes • Unintended consequences • Hospitalisation and health and social care utilisation • Patient reported outcomes (parental satisfaction)
Moltzahn (2012) *Switzerland*	Adults undergoing temporary JJ stenting due to urolithiasis.	Study of prophylaxis of urinary tract infection. Peri-interventional (stent placement) antibiotic prophylaxis (1.2 g amoxicillin/clavulanic acid intravenously) at time of anaesthetic.	Continued low-dose antibiotics.	• Emergence of organisms resistant to antimicrobials • Clinical outcomes • Unintended consequences
Mountokalakis (1985) *Greece*	Newly hospitalised adults with recent stroke and indwelling urinary catheters for urinary incontinence.	Study of prophylaxis of urinary tract infection. 3 g 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.	• Emergence of organisms resistant to antimicrobials • Clinical outcomes
Palmer (2008) *USA*	Critically ill adults requiring mechanical ventilation for >3 days	Study of treatment for ventilator associated tracheobronchitis.	Saline placebo aerosolised.	• 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.		• Clinical outcomes
Palmer (2014) *USA*	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.	• Emergence of organisms resistant to antimicrobials • Clinical outcomes
Revankar (1998) *USA*	Adults with HIV infection.	Study of prophylaxis in community setting. 200 mg of fluconazole orally per day.	Fluconazole (for episodic therapy) dose not defined.	Emergence of organisms resistant to antimicrobials Clinical outcomes
Stahl (1984) *USA*	Girls (aged 2 to 17 years) with symptoms of lower urinary tract infection and 2 sequential urine cultures positive for the same organism.	A study of single-dose treatment for uncomplicated urinary tract infection. A single dose of amoxicillin (50 mg/kg orally maximum 3 g).	Conventional amoxicillin therapy (30 mg/kg/day orally in 3 divided doses for 10 days, maximum per dose 250 mg).	Emergence of organisms resistant to antimicrobials Clinical outcomes
van Zanten (2006) *Netherlands*	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. 2 g of cefotaxime intravenously over 24 hours plus a loading dose of 1 g (over 30 minutes) for 7 days.	1 g of cefotaxime three times daily for 7 days.	Emergence of organisms resistant to antimicrobials Clinical outcomes
van der Wall (1992) *Netherlands*	Adult hospital patients admitted for surgery (vaginal repair, hip replacement or colorectal surgery).	Study of prophylaxis in surgery. Ciprofloxacin 250 mg (plus placebo) once daily Ciprofloxacin 500 mg 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 is not an abbreviation (refers to the pigtail-shaped end of the stent used to secure it).				

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

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

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

5.3.2 Health economic evidence

No health economic evidence was identified for this review question.

5.4 Evidence statements

5.4.1 Clinical outcomes

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

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

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

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

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

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

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

5.4.2 Economic evidence

No health economic evidence for this review question was identified.

5.5 Evidence to recommendations

Table 7: Evidence to recommendations

Relative values of different outcomes	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 (15 studies) of infection. The following interventions were used: • 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)

	• combination therapy (1 study) • watchful waiting (1 study) • statistical process charts (1 study) • post-prescription review (1 study). 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). 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. 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. 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.
Quality of evidence	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. 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. 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. 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.
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 or food and drink
- 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 and medicines optimisation. The GDG concluded that prescribers should take time to discuss with the patient and/or their family members or carers (as appropriate):

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

or if they experience problems as a result of treatment, including any written information provided about this.

The GDG was aware that is it 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) or desirable, if immediate treatment is likely to provide effective management. 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:

- for patients in hospital who have suspected infections, prescribers should take microbiological samples before prescribing an antimicrobial and review the prescription when the results are available
- for patients in primary care who have recurrent or persistent infections, prescribers should consider taking microbiological samples when prescribing an antimicrobial and review the prescription when the results are available
- for patients who have non-severe infections, prescribers should consider taking microbiological samples before making a decision about prescribing an antimicrobial, 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 (where available) 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 2015) 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. 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.
Trade-off between benefits and harms for specific interventions	**Short courses versus longer courses of antimicrobials** 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. 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. 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. The GDG concluded that prescribers should follow local prescribing guidelines and consider prescribing the shortest effective course of antimicrobial treatment. 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. The GDG also acknowledged that in their experience some individuals receiving

antimicrobial prescriptions retained any unused antimicrobials after completing their prescribed course of treatment. These retained antimicrobials were used in self-initiated therapy for subsequent illness without seeking further medical advice.

The GDG noted that there are difficulties in stocking pack sizes of antimicrobials that correspond to treatment guideline course lengths because this varies depending on the infection being treated. Additionally the GDG was aware of the cost implications of manufacturing and purchasing alternative pack sizes (particularly for intravenous and liquid oral formulations). The GDG noted from their experience that in some cases discussions between manufacturers of medicines and provider organisations has led to more appropriate pack sizes becoming available.

The GDG discussed whether supplying pack sizes that correspond to treatment guidelines would lead to more appropriate use of antimicrobials by the people receiving them. The GDG concluded that by taking this approach it would minimise patients retaining unused antimicrobials at the end of a prescribed course for future use.

The GDG agreed that health professionals should prescribe antimicrobials in accordance with treatment guidelines. The GDG also concluded that as a matter of patient safety, organisations should consider supplying antimicrobials in pack sizes that correspond to treatment guidelines on course lengths (for example, pack sizes in urgent care settings or settings in which pre-packaged quantities are supplied).

High versus low dose antimicrobials

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 (where available) and national guidelines and take into account local patterns of resistance.

The GDG concluded that the most appropriate dose for each individual patient should 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 discussed and agreed that ongoing review of prescribing for patients receiving longer term antimicrobial therapy (either for prophylaxis or treatment of infection) is needed. No evidence was found to make a recommendation on the frequency of the review but in its judgement the GDG agreed that the frequency of the review needs to take into account the risk of developing antimicrobial resistance and the additional workload for the prescriber undertaking the review.

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 depending on 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 use of 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 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 search identified a number of RCTs that examined narrower spectrum versus broader spectrum antimicrobials with outcomes that include emergence of resistance. In most cases this was as a secondary outcome of the study and again the results were limited by their power to detect significant differences in the emergence of resistance. The studies were heterogeneous in dose, indication, routes and timing of administration, length of course, comparators, outcomes, setting and population. The studies also had conflicting results. The specific indication and outcomes of the studies placed them outside of the scope of the guideline (recommendations on specific clinical condition are out of scope) and therefore were not included in the review.

The GDG did discuss in their expert opinion the issue of using narrower (or limited) spectrum rather than broad spectrum antimicrobials and whether this was likely to reduce the emergence of resistance, including what the implications would be for clinical practice.

The GDG noted that 'urgent treatment with broad spectrum antimicrobials is life-saving in severe sepsis and septic shock' (CMO Report 2011). The GDG was aware from their experience that broad spectrum antimicrobials are often prescribed before identifying an infecting bacterium; they may also be useful in treating bacterial infections which are resistant to narrower spectrum antimicrobials or in cases of superinfection (an infection caused by more than 1 microorganism).

The GDG was also aware from the CMO Report (2011) that using broad spectrum antimicrobials in preference to narrow spectrum antimicrobials is likely to increase antimicrobial resistance, which can lead to a reduction in the clinical effectiveness of broad spectrum antimicrobials.

The GDG noted that broad spectrum antimicrobials destroy the body's own bacteria (commensal organisms) as well as destroying harmful bacteria. This disruption of the body's own bacteria 'can leave patients susceptible to antibiotic resistant harmful bacteria' (CMO Report 2011) such as *C. difficile*.

Therefore the GDG agreed that, in line with the aims set out in the UK 5 Year Antimicrobial Resistance (AMR) Strategy 2013–2018 (Annual progress report and implementation plan, 2014), when possible the

prescribing of narrow spectrum antimicrobials should be encouraged. The use of broad spectrum antimicrobials should be reserved for those situations where the benefits of their use outweigh the risks of healthcare-acquired infections and the increased risk of resistance.

The GDG recognised that there may be barriers to using narrow-spectrum antimicrobials. For example, a current 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 for patients who need treatment but do not have a definitive diagnosis, organisations should base formulary selection of empirical intravenous antimicrobials on national and local (where available) 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 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 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' records.
Trade-off between benefits and harms after prescribing an antimicrobial	**Documenting decisions** 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. The GDG concluded that when an antimicrobial is a treatment option, prescribers should document in the patients' records: • the reason for prescribing, or not prescribing, an antimicrobial • the plan of care, as discussed with the patient, their family members or carers (as appropriate), including any planned duration of treatment. Where appropriate (for example, in secondary care settings), the GDG agreed, that prescribers should also document any reasons for change of therapy or continued use or stoppage of an antimicrobial. Additionally the GDG agreed that to facilitate audits and monitoring of prescribing, electronic methods of documenting decisions would be advantageous.
Implementation considerations	**Antimicrobial resistance surveillance** 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: • what organism is causing a patient's infection • what antimicrobials would be effective treatment options'.

	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. The GDG agreed that, in line with the 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. The GDG concluded that organisations should provide regular and timely feedback to individual 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) benchmarked against local and national antimicrobial resistance rates and trends • how their antimicrobial prescribing relates to local resistance patterns • hospital admissions linked to previous prescribing decisions in patients with potentially avoidable infections (for example, *Escherichia coli* bacteraemias, mastoiditis, pyelonephritis, empyema, quinsy or brain abscess) • patient safety incidents related to antimicrobial use, including hospital admissions for potentially avoidable life-threatening infections, infections with *C. difficile* or adverse drug reactions such as anaphylaxis. 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, back-up [delayed] prescribing), see section 6.4.1. 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. 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 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. The GDG was aware of resources for commissioners such as those produced by the TARGET initiative.
Economic	No relevant health economic evaluations were found that included

considerations	outcomes of antimicrobial resistance.

5.6 Recommendations and research recommendations

5.6.1 Recommendations

See section 4.1 for a list of all recommendations and appendix F for a summary of the evidence linking the recommendations.

5.6.2 Research recommendations

Uncertainties

This review question considered interventions, systems and processes for reducing the emergence of antimicrobial resistance while not adversely affecting patient outcomes (in the treatment or prophylaxis of infection) compared with usual care or another intervention. The GDG agreed that the systematic review provided limited evidence for this and that a research recommendation would help to address the identified uncertainty.

Uncertainties may be related to:

The clinical effectiveness and cost effectiveness of interventions to reduce the emergence of antimicrobial resistance and maintain patient outcomes in a UK setting.

Reason for uncertainty

The GDG agreed that accurate and unbiased estimates should be obtained of the effectiveness of interventions in reducing the emergence of antimicrobial resistance (a major threat to health) while maintaining patient outcomes.

Randomised controlled trials have investigated the emergence of antimicrobial resistance with:

- short versus longer courses of antimicrobials
- low dose versus higher dose antimicrobials
- directly administered (or observed therapy)
- continuous versus intermittent therapy
- inhaled antimicrobials in addition to systemic therapy.

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

Key uncertainties

The key uncertainty is whether interventions for antimicrobial stewardship reduce or reverse the emergence of antimicrobial resistance and maintain patient outcomes compared with usual care, in a UK setting. The clinical evidence reviewed indicated that for some of these interventions patient outcomes could be maintained while having potential benefits in the reduction of the emergence of resistance.

The GDG suggested that these uncertainties can be addressed by conducting studies that will deliver good quality evidence, such as a randomised controlled trial.

Research recommendation

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

The main outcomes should be patient-related clinical outcomes, unintended consequences as well as the primary outcome of effect on emergence of resistance. The GDG agreed that sample sizes should be calculated to allow accurate assessment of the emergence of antimicrobial resistant organisms.

Other outcomes of interest to the GDG were patient-reported outcomes, health and social care utilisation and the cost effectiveness of the interventions studied.

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

Rationale

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

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

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: • shorter courses compared with longer courses of antimicrobials • higher compared with lower doses of antimicrobials • directly administered (or observed) therapy • continuous compared with intermittent courses of antimicrobials • inhaled antimicrobials in addition to systemic antimicrobials.
Comparator(s)	Well defined routine care or usual care.
Outcome	Outcomes should consider: • patient-related clinical outcomes (for example, treatment success, mortality and secondary infection) • the emergence of organisms resistant to antimicrobials, measured through the development of antimicrobial 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/superinfection • hospitalisation and health and social care utilisation • how closely the individual patients in the study have followed the prescribed course of antimicrobial treatment.
Study design	Randomised controlled trial
Timeframe	A follow up period of at least 2-4 weeks after treatment for acute infection. A follow-up period of 3-12 months for extended courses of prophylaxis or treatment.

6 Decision-making

6.1 Introduction

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

6.2 Review question

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

6.3 Evidence review

6.3.1 Clinical evidence

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

The second search was undertaken to specifically consider point-of-care tests and their possible role in the decision to initiate antimicrobial therapy. Studies from the initial search had been considered and discussed with GDG members who agreed that they did not include point-of-care tests and their possible role in decision-making. The second search was therefore performed specifically for RCTs of point-of-care tests (procalcitonin and C-reactive protein) related to practitioner decision-making. This search identified 5576 references.

After removing duplicates, the references were screened on their titles and abstracts and each included study was identified as being relevant for inclusion for review. Therefore a total of 10,736 titles and abstracts were screened against the inclusion and exclusion criteria as described in the review protocol (appendix C.2). Two hundred and forty-six full papers were ordered and from these, 1 Cochrane review (Spurling 2013) and 11 RCTs (Butler 2012, Camins, 2009, Christakis 2001, Dranitsaris 2001, Fine 2003, Gerber 2013, Gjelstad 2013, Linder 2009, McGregor 2006, Seager 2006, Solomon 2001) met the inclusion criteria for this review. To broaden the search, the reference lists in the systematic review and review papers identified in the search were also searched. This yielded 1 further RCT (Shojania, 1998) that met the inclusion criteria. One further RCT (Lesprit, 2012) was identified by members of the GDG. In total, 13 RCTs and 1 Cochrane review were included.

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

Table 8: Summary of included studies (changing antimicrobial prescribing decisions)

Study	Study type	Population	Intervention	Comparator	Relevant outcomes
Butler (2012) *UK*	RCT	General medical practices	Educational programme – online, face-to-face, clinical practice with reflection	Care as usual	• Antimicrobial use
Camins (2009) *USA*	RCT	Urban teaching hospital	Multidisciplinary antimicrobial utilisation 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)	• Appropriate antimicrobial prescription • Mortality • Length of stay
Christakis (2001) *USA*	RCT	Outpatient teaching clinic	Evidence based prompts – pop-up screens based on their selection of antibiotic, indication and duration	No evidence based prompts	• Duration of therapy
Dranitsaris (2001) *Canada*	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	• Appropriate antimicrobial prescription
Fine (2003) *USA*	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	• Duration of therapy • Length of stay
Gerber (2013) *USA*	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	• Antimicrobial use
Gjelstad (2013) *Norway*	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	• Antimicrobial use
Lesprit (2012)	RCT	University hospital	Post-prescription review by infectious disease physician in addition to	Antimicrobial stewardship programme, no prescription review	• Duration of therapy

Study	Study type	Population	Intervention	Comparator	Relevant outcomes
France			antimicrobial stewardship programme		• Mortality • Length of stay
Linder (2009) *USA*	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	• Antimicrobial use
McGregor (2006) *USA*	RCT	Tertiary care referral centre	Antimicrobial management team – infectious diseases physician and pharmacist	Standard care	• Mortality • Length of stay
Seager (2006) *UK*	RCT	General dental practitioners	Educational material (by post); guidelines, laminated page summary, patient information leaflets Educational material and academic detailer	No intervention	• Antimicrobial use • Appropriate antimicrobial prescription
Shojania (1998) *USA*	RCT	Tertiary care hospital	Computer based intervention, showing computerised guidelines for ordering	Usual screen computer	• Antimicrobial use • Duration of therapy
Solomon (2001) *USA*	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	• 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	• Antimicrobial use • Adverse effects

Table 9: Summary of included studies (point-of-care tests)

Study	Study type	Population	Intervention	Comparator	Relevant outcomes
Procalcitonin (PCT)					
Baer (2013) *Switzerland*	RCT	1 month to 18 years, lower respiratory tract infection	Treatment based on PCT categories, assay time <30 minutes, emergency department	Treatment based on physician assessment and clinical guidelines	• Antimicrobial use
Esposito (2011) *Italy*	RCT	1 month to 14 years, community-acquired pneumonia	PCT guided decision to treat	Treatment guided by guidelines	• Antimicrobial use
Manzano (2010) *Canada*	RCT	1 month to 36 months, 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) *USA*	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

6.3.2 Health economic evidence

A systematic literature search (appendix C1.2.2) was undertaken to identify cost-effectiveness studies evaluating systems, interventions and processes that change health and social care practitioners' decision-making to ensure appropriate antimicrobial stewardship. This search identified 2523 records, of which 2501 were excluded based on their title and abstract. The full papers of 22 records were assessed and 19 were excluded at this stage. The excluded studies and reason for their exclusion is shown in appendix C.5.2.

The 3 studies meeting the inclusion criteria were quality assessed using the NICE quality assessment checklists for cost-effectiveness studies. Two additional studies were identified and assessed after discussion with the GDG and following consultation on the draft guideline; 1 study (Hunter 2015) was subsequently included.

The study by Jensen et al. (1997) is a US cost-effectiveness study of abbreviated intravenous therapy. The study has minor limitations. It was deemed partly applicable because no UK studies or studies better matching the NICE reference case were identified; additionally the study population was a subgroup of the guideline population and a US healthcare system perspective was taken. It is based on data from 2 RCTs.

The US study by McGregor et al. (2006) examined the costs and consequences of a hospital antimicrobial stewardship team supported by computerised clinical decision support. It was deemed partially applicable to the guidance, despite major limitations. It consists of a cost-consequences analysis rather than cost-effectiveness analysis that the authors report. The US study by Scheetz et al. (2009) is a cost-utility analysis of the same intervention which has only minor limitations. This study was also deemed partially applicable. In both studies the study population was a subgroup of the guideline population and a US healthcare system perspective was taken.

The UK study by Hunter (2015) is a decision analytic model of the use of point-of-care C-reactive protein in a general practice setting. It was deemed partially applicable to the guideline because the study population, those with respiratory tract infection, is a sub-group of the population covered by the guideline.

The 4 studies were judged to be suitable for inclusion. These are summarised in Tables 10 to 12. The study evidence tables for the included studies are shown in appendix D.1.3 and quality assessment tables in appendix D.2.2.

Table 10: Economic evidence profile – abbreviated IV antibacterial therapy

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effects	Cost effectiveness	
Jensen, et al. (1997) Cost effectiveness of abbreviating the duration of intravenous antibacterial therapy with oral fluoroquinolones	Minor limitations[1, 2]	Partially applicable[3, 4]	Randomised controlled trial data from 2 trials informed a decision tree model.	At level 4[5] the mean cost ± SEM was: Intervention:$4818 ± $269 Control: $5028 ± $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 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 of the guideline population, although not a UK population.
[4] US health care system (payer perspective).
[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 that 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.

Table 11: Economic evidence profile – antimicrobial management team with computerised clinical decision support system

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effects	Cost effectiveness	
McGregor et al. (2006) Impact of a computerised clinical decision support system on reducing inappropriate antimicrobial use: a randomised controlled trial	Major limitations[1, 2, 3]	Partially applicable[4, 5]	Authors state that this is a cost effectiveness-analysis. 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 the 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 *C. difficile*, though the difference was not statistically significant [8]. There were also no significant differences in the number of positive *C. difficile* 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 et al. (2009) Cost-effectiveness analysis of an antimicrobial stewardship team on bloodstream infections: a probabilistic analysis	Minor limitations[10, 11]	Partially applicable[4, 12]	Decision analytic model with data identified by a systematic review of the literature (experimental and observational studies and 1 clinical guideline report)	**Total cost (Base case)** Intervention: $40144 Standard treatment: $39776	**Total QALYs (Base case)[13]:** Intervention: 8.01 QALYs Comparator: 7.92 QALYs	$4089 per QALY[14, 15]	One-way sensitivity analysis: Non ICU[16] ICERs that 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

Study	Limitations	Applicability	Other	Incremental			Uncertainty
							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 of 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 a literature search.
[11] Estimates of unit cost were obtained from a 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.
[16] Probability of receiving an active antibiotic on general floors (non-ICU care).

Table 12: Economic evidence profile – point-of-care C-reactive protein (POC CRP) testing in adults with RTI

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effects	Cost effectiveness	
Hunter, R (2015) Cost-effectiveness of point-of-care C-reactive protein tests for respiratory tract infection in primary care in England.	Major limitations[1, 2, 3]	Partly applicable[4]	Decision analytic model; it is uncertain how the data that informed the model were identified[5], and whether any quality appraisal was conducted of the included	**Total cost (discounted) over 3 years per 100 patients:** Current practice: £18,081 GP plus POC CRP: £18,039 PN plus POC CRP: £17,401 GP plus POC CRP and communication: £18,431	**QALYs (discounted) over 3 years per 100 patients:** Current practice: 255.630 GP plus POC CRP: 255.764 PN plus POC CRP: 255.761 GP plus POC CRP and communication: 255.588 **Antibiotics prescribed (courses) over 3 years per 100 patients:**	**Probability cost-effective:** In a probabilistic sensitivity analysis, at a willingness to pay (WTP) of £20,000 per quality-adjusted life year (QALY), GP plus CRP has a higher net monetary benefit than current practice for 77% of iterations and practice nurse plus CRP has a higher NMB than current practice for	**Analysis of uncertainty:** In probabilistic sensitivity analysis (3 year time horizon, 100 patients and 1000 iterations) the GP plus CRP test strategy is dominant (costs less and results in more QALYs) compared with current practice in 50% of simulations; in 65% of simulations the practice nurse plus CRP test strategy is dominant

Study	Limitations	Applicability	Other	Incremental		Uncertainty
			studies.	Current practice: 184 GP plus POC CRP: 136 PN plus POC CRP: 167 GP plus POC CRP and communication: 137 **Infections over 3 years per 100 patients:** Current practice: 217.89 GP plus POC CRP: 202.97 PN plus POC CRP: 202.97 GP plus POC CRP and communication: 199.98	82% of iterations in the analysis.	and in 19% the GP plus CRP and communication training strategy is dominant.

[1] The model does not include all appropriate interventions as it does include a practice nurse who is an independent prescriber using POC CRP.
[2] The Markov model only includes 2 health states (healthy and respiratory tract infection) and excludes the possibility of death from infection in a hypothetical cohort with an average age of 50 years. The authors' model assumes that the only way a patient can die is following an antibiotic related adverse event.
[3] The author reports that only the incremental costs of performing a CRP test are included. This would be justified in a European context where POC CRP testing in primary care is more common (i.e. the initial cost of purchase and maintenance of an analyser has already been made). However in a UK setting where it is less common to have these machines already these are potentially important costs that have not been included.
[4] The patient population (patients seen in general practice with respiratory tract infection) is a subgroup of the guideline population.
[5] Possible issues of bias in included studies and data, also no information on whether the author examined the available literature for publication bias.

6.4 Evidence statements

6.4.1 Clinical evidence

Outcomes

Antimicrobial use

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

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

Appropriate antimicrobial use/selection of antimicrobial

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

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

Duration of therapy

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

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

Mortality

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

- Antimicrobial stewardship or management programmes/multidisciplinary team review was used in 2 studies (in secondary care); no differences in mortality were found between the intervention and control groups.
- Clinical education/academic detailing was used in 1 study (in secondary care); no differences in mortality were found between the intervention and control groups.

Point-of-care tests

One individual patient data meta-analysis (low quality) in adults with acute respiratory infection found decreased initiation of antibiotic therapy with those using procalcitonin-guided cut-off ranges compared with those using standard care.

Three RCTs (very low quality) involving children, found no difference in antibiotic use between those having procalcitonin-guided therapy and those having standard care.

One individual patient data meta-analysis, in adults with respiratory infections, found no difference in mortality with those using procalcitonin-guided cut-off ranges to initiate antibiotic therapy compared with those using standard care.

One meta-analysis of 4 RCTs (very low quality), in those with acute respiratory infection, found decreased antibiotic prescribing with those using C-reactive protein-guided antibiotic therapy compared with those using standard care. One RCT (very low quality), in adults with acute cough, found no difference in antibiotic prescribing between those using C-reactive protein-guided treatment along with a management algorithm compared with those using the management algorithm alone.

6.4.2 Economic evidence

Partially applicable evidence with minor limitations built on RCT data suggests that abbreviating the duration of intravenous antibacterial therapy with oral fluoroquinolones is likely to be a cost-effective use of NHS resources.

No relevant evidence was identified informing the cost effectiveness of the use of other types of switch therapy other than the fluoroquinolones modelled in the study.

Partially applicable evidence from 2 studies, 1 with minor limitations built on systematic review data and 1 with major limitations built on RCT data, suggests that an antimicrobial stewardship team with computerised clinical decision support is likely to be a cost-effective use of NHS resources.

Partially applicable evidence with major limitations from RCT data suggests that in general practice for patients with respiratory tract infection point-of-care testing for C-reactive protein by a GP or practice nurse is likely to be a cost-effective use of NHS resources where the necessary equipment to undertake point-of-care testing for C-reactive protein is already available.

6.5 Evidence to recommendations

Table 13: Evidence to recommendations

Relative values of different outcomes	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.

	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. 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. The GDG discussed the evidence in terms of the implications for both patient outcomes and costs relating to length of patient stay in hospital. 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.
Trade-off between benefits and harms	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. 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 although 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: • clinical education/academic detailing • computer-based decision support/guidelines • antimicrobial stewardship/management programmes or multidisciplinary team prescribing review • clinical pharmacist review • educational outreach • back-up (delayed) prescribing • point-of-care testing. The GDG discussed computer-based decision support and the role these systems may have in the decision-making process, particularly for reminding and informing prescribers in both primary care (including dentistry) and

secondary care about possible prescribing choices. The GDG believed efficiency was likely to be a key benefit of these systems, through reminders to prescribers. The GDG noted that in future it may be possible for these systems to:

- link to electronic prescribing systems while highlighting local (where available) or national antimicrobial formulary prescribing options (for example, IV to oral antimicrobial prescribing options)
- link individual patients' microbiological results to prescribing options
- support for health professionals through the provision of patient information (patient information leaflets).

The GDG also agreed there was an opportunity for these systems to have search functions to allow for improved audit capability.

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, it 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 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 should enable effective challenge or questioning of 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. There should also be flexibility to prescribe outside 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 is apparent. 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 back-up (delayed) prescribing for those with respiratory tract infections. The GDG noted that these studies provided consistent evidence that back-up (delayed) prescribing reduced antimicrobial prescribing and did not show increased adverse events or reduced patient satisfaction. GDG members noted the lack of evidence for back-up (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 back-up (delayed) prescribing could be recommended as part of antimicrobial stewardship.

The GDG was aware that the term delayed prescribing has limited understanding by the general population. 'Back-up prescribing' is now being used as an alternative term, suggesting that this approach is a fall back strategy rather than an assumption that a prescription will be issued at some point in the future (as the term 'delayed prescribing' suggests). The GDG also

agreed the need to discuss the reasons for using back-up (delayed) prescribing with patients or carers, and the need for advice on re-consultation if symptoms change.

The GDG was aware that the implementation of Electronic Prescription Services (EPS) may allow review of whether back-up (delayed) prescriptions have been supplied by the pharmacy, measuring the impact of back-up prescribing through local audit and at wider regional or national level.

The GDG was aware from their knowledge and experience that most of the evidence on point-of-care testing relates to respiratory tract infection. The GDG included those point-of-care studies likely to be of sufficient methodological quality (such as RCTs) to amend or add to the evidence and recommendations set out in the NICE guideline on pneumonia (published December 2014). For example, any RCTs including point-of-care testing for conditions other than respiratory tract infection.

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. In relation to this review question, evidence was identified for procalcitonin (PCT) and C-reactive protein (CRP) point-of-care tests. The GDG noted that in the NICE guideline on pneumonia it was recognised that 'point-of-care testing for CRP or PCT is not widely used in the UK at present, and that the introduction of their use would represent a significant change in practice. As such, there would be significant costs associated with training, implementation and subsequent quality assurance of equipment'.

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 prescribing 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 any point-of-care test to be compared with current clinical assessment (both in primary care and in emergency departments) or the use of interventions such as delayed (back-up) prescribing that reduce prescription rates without any additional time and cost resources associated with a 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) to show that these tests reduce inappropriate prescribing compared with other methods.

The GDG also discussed whether offering point-of-care tests would medicalise self-limiting conditions for which self-care should, in most cases, be the first approach to treatment. The GDG also discussed whether point-of-care tests would encourage patients to request an appointment to have the test, when otherwise they would self-manage their infection (re-consultation). The GDG agreed that there was still uncertainty as to whether longer follow-up by clinical studies of point-of-care testing would demonstrate increases or reductions in re-consultation. It was noted by the GDG that uncertainty on re-consultation and hospitalisation was also discussed by the Committee developing the NICE guideline on pneumonia. The pneumonia guideline states that aside from the 'real life experience of these tests' being limited outside of clinical studies another area of uncertainty related to apparent increases in 'hospital admissions and re-consultation rates associated with point-of-care testing'. The

NICE guideline on pneumonia states that included studies 'were not able to demonstrate whether this increase in healthcare utilisation was appropriate (with sick patients flagged up correctly, reducing overall harm) or inappropriate (with increased anxiety and healthcare utilisation in patients who would have had a good outcome without point-of-care testing). With large-scale implementation of point-of-care testing, these differences could have significant financial implications which could potentially outweigh the benefits of reduced antibiotic prescribing.'

The GDG was aware that the economic study by Hunter (2015) does take account of some of the uncertainty regarding the cost of hospital admissions for point-of-care C-reactive protein test strategies compared with a no test strategy. However, the GDG agreed that uncertainty remains over the nature of the apparent increases in admissions (whether they are appropriate or not) and the resulting opportunity cost for those additional admissions from point-of-care C-reactive protein testing. The GDG discussed the implications of potentially inappropriate admissions and constrained NHS hospital resources.

The GDG discussed the findings from the Hunter (2015) economic study that addressed some of the uncertainty regarding communication skills training identified in the NICE guideline on pneumonia. The economic model included a strategy of GP consultation plus point-of-care C-reactive protein test plus communication skills compared with usual care and GP or practice nurse plus point-of-care C-reactive protein test strategies. In deterministic analysis, the strategy including communication skills was associated with increased costs and reduced quality-adjusted life years (QALYs) compared with other strategies, including current practice. The GDG was aware, however, that this strategy was associated with a low number of antibiotics prescribed (137 courses versus 184 for usual care, 167 for practice nurse plus point-of-care C-reactive protein testing and 136 for GP plus point-of-care C-reactive protein) and the lowest number of infections for any strategy in the model (results for 3 years per 100 patients). Therefore, in line with the NICE guideline on pneumonia, the GDG wished to emphasise the importance of communication skills in the prescriber–patient interaction.

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

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. 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. 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 inspectors for essential standards.
Economic considerations	In relation to point-of-care tests, there was 1 economic study (Hunter 2015) identified that met the inclusion criteria for this review question. The GDG noted that the study found that 2 of the 4 strategies in the model (GP consultation with point-of-care C-reactive protein test and practice nurse consultation with referral to GP after the test) were likely to be cost effective for diagnosing respiratory tract infection in primary care compared with usual GP care or GP plus communication skills training. The GDG also noted that not all relevant, competing strategies were included in the model (for example, there is no strategy for practice nurse with independent prescribing qualification in the model and also no comparison with other point-of-care or near-patient tests such as procalcitonin testing). An additional limitation of the study noted by the GDG is that it does not appear to include the costs for purchase or maintenance of the analyser used in the model. The GDG noted that because of uncertainty in the model it was unable to state which of the 2 strategies would be more cost effective in practice. The GDG was aware, however, that in the deterministic analysis (results for 3 years per 100 patients) the estimated number of antibiotic courses prescribed was lowest in the GP consultation plus point-of-care C-reactive protein test strategy. GDG members agreed that this had implications for the development of antimicrobial resistance. The GDG reviewed the related economic evidence and discussion considered in the NICE guideline on pneumonia because it agreed that this allowed for a comparison between alternative point-of-care tests. The pneumonia guideline 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 testing was considered to be cheaper than procalcitonin testing and more clinically useful. The GDG agreed that this conclusion was reasonable.
Quality of evidence	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.
Other considerations	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 they discussed whether 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. 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 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.

6.6 Recommendations and research recommendations

6.6.1 Recommendations

See section 4.1 for a list of all recommendations and appendix F for a summary of the evidence linking the recommendations.

6.6.2 Research recommendations

Uncertainties

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

Uncertainties may be related to:

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

Reason for uncertainty

The search identified a small number of studies relating to the use of C-reactive protein or procalcitonin point-of-care tests compared with standard care/guidelines in those presenting with respiratory tract infections. The clinical evidence reviewed indicated that the use of these tests could reduce antimicrobial use without leading to an increase in re-consultations or reduced patient satisfaction.

Key uncertainties

Point-of-care tests have been used to reduce prescribing of antimicrobials. There were no studies identified in the review for this guideline that considered the effectiveness of point-of-care tests when compared with other interventions that may reduce prescribing. Furthermore, these other interventions (such as the use of back-up [delayed] prescribing) may be non-invasive and may require less practitioner time and/or training. The GDG suggested that randomised controlled trials would be appropriate for further comparison of point-of-care tests with other methods for reducing antimicrobial use.

Research recommendation

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.**

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

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

Rationale

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

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

Uncertainty in this area may be answered by conducting a study that is sufficiently powered and will deliver good quality evidence, such as a randomised controlled trial.

PICO format:

Criterion	**Explanation**
Population	Those with respiratory tract infections
Intervention	Point-of-care tests used immediately before (<60 minutes) or during consultation
Comparator(s)	Use of back-up (delayed) prescribing Other methods for reducing antimicrobial use Usual care
Outcome	Outcomes to be included should consider: • 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 patients presenting to primary care or hospital admission. For results to be valid and reliable, outcomes should ideally be measured using validated tools, and where this is not possible the method for measuring outcome should be detailed in the study.
Study Design	Randomised controlled trial
Timeframe	3 months

7 Barriers to decision-making

7.1 Introduction

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

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

7.2 Review question

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?

7.3 Evidence review

7.3.1 Clinical evidence

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

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

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

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

Available data were extracted into evidence tables (see appendix D.1.4) and are summarised in table 14 below:

Table 14: Summary of included studies for the review question on barriers to decision-making

Study	Population	Study type	Key results
Abbo (2013) *USA*	Clinicians from 82 acute care facilities	Cross-sectional study	The following barriers to implementation were identified: • Lack of time. • Personnel shortages. • Inadequate funding.
Bannan (2009) *Australia*	256 clinicians from the Concord hospital	Cross-sectional study	Key findings identified were: • 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) *Australia*	30 doctors who prescribe antibiotics at a hospital	Qualitative: semi-structured interviews	Barriers identified included: • 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) *England*	39 health professionals from 4 hospitals	Qualitative: semi-structured interviews	The following barriers were identified: • 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.
Cortoos (2008) *Belgium*	22 participants from a tertiary care teaching hospital	Qualitative: focus groups	Two key barriers were identified: • Prescribing practices of juniors are strongly influenced by supervisors. • Pressure of work limited time to consult guidelines.
De Souza (2006) *Ireland*	22 participants from a 500 bed university teaching	Qualitative: semi-structured interviews	From the analysis 3 key findings are relevant: • Senior colleagues have the most significant influence on prescribing practices.

Study	Population	Study type	Key results
	hospital		• 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 study	Barriers to implementation included: • Staffing constraints. • Insufficient staff buy-in. • Competing priorities.
Hart (2006) *USA*	21 primary care clinicians	Qualitative: semi-structured interviews	A key finding was: • 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: • 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: • 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: • 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 specialities antagonised by ASP. Multiple infectious disease groups within the facility. 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.
Kumar (2003)	40 GPs	Qualitative: semi	Decision-making:

Study	Population	Study type	Key results
England		structured interviews	The presence of adverse social factors lowered general practitioners' threshold for prescribing antibiotics for sore throat: • Clinical experience, length of service, and research evidence. • Antimicrobial resistance. • Maintaining patient/doctor relationship.
Schouten (2007) *Netherlands*	18 care providers	Qualitative: semi-structured interviews	The authors suggest interventions to overcome guideline barriers: • 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) *Wales*	40 GPs	Qualitative: semi-structured interviews	Agreed AMS is a problem but they infrequently encountered its consequences (microbial resistance) locally. Suggested • More information about resistance patterns locally. • Enhanced practitioner training.
Teo (2013) *Australia*	5 antimicrobial stewardship committee members (policymakers) and 15 prescribers	Qualitative: semi-structured interviews	Barriers to compliance with the antibiotic prescribing policy: • Lack of knowledge. • Inapplicability of the antibiotic prescribing policy. • Prescriber autonomy and personal experience. • Organisational hierarchies. Overcoming barriers: • Involving prescribers in policy development. • Giving feedback about their prescribing. • Improving existing collaboration and decision support platforms.
Wigton (2008) *USA*	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%). • 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
			The authors suggest that these situations would be important areas for practitioner education.
Wood (2007) *Wales*	40 GPs	Qualitative	The study looked at GP surgeries with differing levels of prescribing broad spectrum antibiotics (fluoroquinolones). • 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. 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.

7.3.2 Analysis of the included studies

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

- Clinical priorities
  - data
  - resistance patterns
  - prescribing patterns
  - feedback to prescribers
  - competing priorities.
- Decision-making
  - knowledge
  - judgement
  - patient expectations
  - values.
- Hierarchies or social structures
  - knowledge and judgement
  - willingness to challenge practice.
- Resources
  - time
  - staffing
  - funding.

Because of the methods used in the included studies (cross-sectional and qualitative), the use of the GRADE was not considered appropriate. The NICE checklist for qualitative studies was used. A checklist originally published in the British Medical Journal (see appendix H) was used to aid in the quality assessment of the cross-sectional surveys. The search results did not identify studies directly considering interventions, systems or processes to overcome barriers to decision-making by health and social care practitioners when ensuring appropriate antimicrobial stewardship. Evidence to demonstrate their effectiveness or cost effectiveness was also not found. Studies included in the analysis identified barriers to appropriate antimicrobial stewardship and some suggested interventions, systems or processes that may be effective in overcoming these barriers. Therefore, 2 key themes matrices were used to present the key themes from the included studies. One (see table 15) summarises the barriers to decision-making and the other (see table 16) summarises key themes that were identified as potential considerations for overcoming the identified barriers.

Table 15: 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 their patients to be "outside" the	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
		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 consequences [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.			

Table 16: 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
		practice and some questioned the evidence linking their prescribing decisions to resistance and poorer outcomes for their patients. Undergraduate and graduate education about antimicrobial prescribing and resistance should be enhanced		
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)		Based on hypothetical cases of acute respiratory tract infection, community practitioners prescribed antibiotics at twice the rate of a faculty following CDC practice guidelines. 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.		

7.4 Health economic evidence

No health economic evidence was identified for this review question.

7.5 Evidence statements

7.5.1 Clinical evidence

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

- lack of time
- insufficient of funding
- inadequate staffing.

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

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

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

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

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

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

7.6 Evidence to recommendations

Table 17: Evidence to recommendations

Relative values of the different barriers identified	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. **Decision-making when prescribing an antimicrobial** 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

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 back-up (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, back-up [delayed] prescribing).

Hierarchical 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.

The GDG also discussed the role of the antimicrobial stewardship team (AMS team) with regard to educating prescribers. The GDG agreed that the role of the AMS team would primarily be to promote antimicrobial stewardship education at the prescriber level. Although some AMS team members may wish to participate in more formal education programmes, such as delivery of workshops or classroom teaching, the GDG recognises that not all AMS team members will have the prerequisite educational skills or the necessary resources to deliver relevant education to prescribers.

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.

The GDG discussed whether organisations should feedback to prescribers about both national and local data. The GDG agreed that where possible prescribers should be able to compare their prescribing data with local and national comparators. The GDG recognised comparisons between local prescribers with perhaps similar populations as a benchmark but that comparison at a national level would allow prescribers and organisations to see how they benchmarked against prescribing nationally, with a view to reducing national variation in prescribing of antimicrobials. The GDG was aware that different comparator populations (either local or national) may have dissimilar demographics (for example, different areas may have different population age, gender, burden of illness or levels of deprivation), but the GDG was aware that there is currently ongoing work to provide better comparator data.

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 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 interventions can be documented either electronically and/or on paper, and not all practices use the same method. Furthermore, there are no reason codes 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, and prescriptions continue to be hand written. The GDG was aware 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 benefits and harms	The evidence identified some barriers to decision-making in relation to antimicrobial stewardship. Some of the evidence suggested interventions to overcome these, but the interventions were not assessed for effectiveness in the studies.
Resource considerations	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. 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. 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 that an effective antimicrobial stewardship programme can have. 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.

	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.
Quality of evidence	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. 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.
Other considerations	**Antimicrobial stewardship programmes** 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 to antimicrobial stewardship programmes identified in the evidence. 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, and 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 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). However the GDG agreed that commissioners should ensure that antimicrobial stewardship operates across all care settings as part of the antimicrobial stewardship programme. Additionally the GDG discussed who should comprise an antimicrobial stewardship team. The GDG agreed that membership of an antimicrobial stewardship team would be dependent upon the knowledge, skills and experience of individuals rather than a specific job role (which may or may not be relevant to all organisations) and could include a range of clinicians from different settings. However, the GDG concluded that core membership of an antimicrobial stewardship team should include an antimicrobial pharmacist and a medical microbiologist. 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 potentially avoidable life-threatening infections, infections with *C. difficile* or adverse drug reactions such as anaphylaxis • providing education and training to health and social care practitioners about antimicrobial stewardship and antimicrobial resistance • integrating audit into existing quality improvement programmes. The GDG discussed how some of the barriers identified in the evidence

could affect the implementation of an effective antimicrobial stewardship programme, including how a programme could be delivered in practice. The GDG was aware that providing education and training to health and social care practitioners about antimicrobial stewardship and antimicrobial resistance across all care settings would be challenging but agreed that various methods could be used to address this challenge (for example, the use of workshops and the development of online tools for continuing professional development. 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 try to communicate

	consistent messages about antimicrobial stewardship.

7.7 Recommendations and research recommendations

See section 4.1 for a list of all recommendations and appendix F for a summary of the 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 in 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' antimicrobials into the NHS?

The term 'new' antimicrobial includes:

- a new antimicrobial

- a newly marketed formulation of an existing antimicrobial
- an antimicrobial that is licensed but not available on the NHS.

8.3 Evidence review

8.3.1 Clinical evidence

A systematic literature search was conducted (see appendix C.1.2.4) and identified 2489 references. After removing duplicates, the references were screened on their titles and abstracts to identify studies relevant for inclusion in the review. No references were obtained and reviewed against the inclusion and exclusion criteria as described in the review protocol for the timely adoption and diffusion of new antimicrobials into the NHS (appendix C.2.4). However, 7 partially applicable non-research articles were obtained for background information. These provided information on organisational approval processes for new antimicrobials, implementation planning for the introduction of a new antimicrobial and decisions to restrict access to a new antimicrobial (see section 9 [references] and table 20 for a summary of the key themes).

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

Table 18: Summary of included studies for the review question on the timely adoption and diffusion of a new antimicrobial

Study	Population	Intervention	Comparison	Key critical and important outcomes
McNulty (2011)[1] *England*	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

8.3.2 Additional evidence

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

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

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

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

Table 19: Summary of information received from the call for evidence

Question	Summary of respondents' information
Does your organisation have a process for the adoption of new medicines?	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. 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. 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.
Does your organisation have a different process for the adoption of new antimicrobials? If so how and why?	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. The committee membership (where described) most often comprised: • a consultant microbiologist • an infectious diseases consultant • an antimicrobial pharmacist. In some cases there was representation on the group from outside 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: • the need for monitoring the use of the new antimicrobial

Question	Summary of respondents' information
	• 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 antimicrobial in therapy. 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.
How do you use the antimicrobial once adopted? For example, do you restrict prescribing or is it freely available?	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: • a prior approval process with permission sought from a consultant microbiologist or similar • use being limited to certain specialties (for example, intensive care units) • use limited to specialist initiation • use requiring post-prescription specialist review • local restriction of new antimicrobials communicated to prescribers through the use of guidelines, formulary and clinical commissioning group prescribing recommendations in primary care.
Do you produce an implementation plan to support appropriate prescribing once it is approved for use?	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. The most commonly cited methods of implementation planned for new antimicrobials in secondary care were: • alerts via e-mail and through intranet to prescribers • new or updated guidelines for prescribing and formulary

Question	Summary of respondents' information
	• individual peer to peer advocacy as required • guidance specific to the new antimicrobial for prescribers • educational interventions for appropriate specialty teams, informal teaching on ward rounds or post-antimicrobial audit educational visits • laboratory support for prescribers.
If so what criteria does this include?	Where implementation plans are used, common information for prescribers included: • 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 and review dates • any advantages or disadvantages compared with 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?	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. Many respondents both in primary and secondary care stated that barriers causing the main delays were pre-adoption (committee processes and bureaucracy) because 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 because of multiple, sequential committee processes). However, a number of respondents noted that prescribers were often reluctant to change their practice, perhaps because of a 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 antimicrobial to prescribers. 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

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 while 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.	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). 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: • 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 antimicrobial 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 antimicrobial 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?	No respondent organisation has measured changes in resistance resulting from changes in processes for approval of new antimicrobials. Additionally where resistance data have been collated over time, respondents state that it would be very difficult to isolate the effects of a single process, such as an approval process, in terms of resistance to a new antimicrobial, because the organisations will have multiple processes of stewardship and infection control running concurrently. In general, more monitoring was being conducted in secondary care. 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.
What barriers do you think exist for	Most respondents cited the cost of new antimicrobials as a barrier to their introduction. New medicines usually cost more than the ones they are meant to replace or supplement. Several respondents state they use these newer antimicrobials only in specific cases (such as

Question	Summary of respondents' information
the introduction of a new antimicrobial? Please give brief examples	high-risk cases or older people) because of cost considerations. The respondents also cited a concern about a lack of evidence for some new antimicrobials. This was a real concern for several respondents, who state that clinicians are reluctant to start the use of new antimicrobials early if there are insufficient data on safety. Data on dosing and safety were felt to be lacking for particular populations such as children, neonates and older people, which 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, for which the respondent stated several years were taken 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. Another concern was that newer antimicrobials may not have a clinical advantage over current therapies and that often the newer therapy may come at a substantially higher cost. A further concern regarding the effectiveness of new antimicrobials was raised by 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 was an issue (for example, pivmecillinam, temocillin, caspofungin and voriconazole [versus amphotericin B] in the treatment of an unspecified haematological condition). Concern was raised by respondents about the licensed formulations of antimicrobials available for treating certain conditions (commonly the example of the formulation of fosfomycin available for the treatment of extended spectrum beta-lactamase urinary tract infections). 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. A point was raised by 1 respondent about the effects of restricting access to new antimicrobials for the purposes of stewardship, which relates to the selection of particular patients in whom these locally restricted antimicrobials are subsequently used. Typically, valuable new antimicrobials are restricted for use. The respondent reports that restrictions are mainly put in place for antimicrobial stewardship reasons. However, the respondent states that these restricted antimicrobials are used in selected clinical cases or certain specialties 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

Question	Summary of respondents' information
	of their use in practice. A small number of respondents discussed the impact of delays in the national approval (by NICE or the Scottish Medicines Consortium) and/or licensing delays from the European Medicines Agency (EMA) or the Medicines and Healthcare products Regulatory Agency (MHRA).
When considering whether to adopt a new antimicrobial, to what extent are patient/carer views considered?	Most respondents stated that their processes for the approval of a 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 with 3 doses of an existing antimicrobial) and any issues with adherence to the new antimicrobial. 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.
If an antimicrobial has been 'rejected for routine use' or restricted, how is this decision reviewed, particularly considering antimicrobial availability?	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 variation in practice from the responses given to this question and a few respondents stated that decisions were not reviewed or there was no formal process for review in place. 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.

Table 20: 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) *USA*	Formulary decisions: • route of administration		Issue of high-level cross resistance (such as

Study	Organisational approval processes for new antimicrobials	Implementation planning for the introduction of a new antimicrobial	Decisions to restrict access to a new antimicrobial
	• contraindications • cautions • adherence • dose adjustment • tolerability (adverse effects) • drug interactions.		resistance to new antimicrobial because of resistance to older antimicrobials of the same class)
Keegan (2001) *USA*	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) *UK*		Suggests GP attitude to guidance is 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 review 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) *UK*	Formulary decisions: • Costs (not just acquisition cost), that is, monitoring costs, likely subsequent outcomes and adverse events costs. • Effectiveness - pharmacological efficacy (in vitro).		

Study	Organisational approval processes for new antimicrobials	Implementation planning for the introduction of a new antimicrobial	Decisions to restrict access to a new antimicrobial
	• 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) *Spain*	Formulary decisions: • 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) *USA*	Formulary decisions: • Effectiveness - pharmacological efficacy (in vitro). • Safety information. • Costs (not just acquisition cost), that is, monitoring costs, likely subsequent outcomes and adverse events costs.	Risk assessment and risk management strategies for use of potentially useful but 'problematic drugs'. Systems and processes should be in place to allow the prescription of non-formulary drugs when a clinical situation dictates this necessity. Managed introduction based on the amount of education or pre-introduction work (protocols, pre-approval processes, drug safety processes) that needs to be undertaken.	Prior approval for medicines with greater risks or limited to certain specialities or settings.
Tam (2006) *USA*	Formulary decisions: • Input from experts with knowledge of		

Study	Organisational approval processes for new antimicrobials	Implementation planning for the introduction of a new antimicrobial	Decisions to restrict access to a new antimicrobial
	local patterns of resistance needed. • Place in therapy. • Dosing regimen. • Costs (not just acquisition cost), that is, monitoring costs, likely subsequent outcomes and adverse events costs.		

8.3.3 Health economic evidence

No health economic evidence was identified for this review question.

8.4 Evidence statements

8.4.1 Clinical evidence

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

8.4.2 Call for evidence

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

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

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

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

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

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

Organisations identified a number of barriers to the rapid adoption of new antimicrobials. These included organisational processes (for example, the need for multiple committees to approve a new medicine), prescriber inertia (linked to the delay between an approving committee approving a new antimicrobial and providing support to prescribers with updated

guidance and formulary) and internal and external funding agreements (departmental funding or funding for Payment by Results [PbR] excluded medicines).

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

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

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

8.4.3 Economic evidence

No health economic evidence was identified for this review question.

8.5 Evidence to recommendations

Table 21: Evidence to recommendations

Quality of evidence	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, because of the lack of concurrent control it was less robust than evidence from a randomised controlled trial. The call for evidence provided the GDG 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 variation in current practice and the background papers from which key themes were extracted.
Trade-off between benefits and harms Organisational approval processes for new antimicrobials	**Decision-making bodies** Decisions relating to new medicines for local approval and inclusion in 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. 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). The GDG inferred 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.

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), 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 medical microbiologist and an antimicrobial pharmacist, examples of those who may be included in a decision-making process were:

	• a community practitioner • someone with commissioning responsibility • 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. **What should be reviewed by the decision-making body?** 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. The GDG, based on a discussion of the information received in response to the call for evidence and other summary articles (see tables 18 and 19), 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: • the need for the new antimicrobial • clinical effectiveness • 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. **Reviewing and updating the need for a new antimicrobial** 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: • new evidence or surveillance data • new or increased use of the new antimicrobial outside 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. 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.
Trade-off between benefits and harms for decisions to restrict new antimicrobials	**Decision-making bodies restricting the prescribing of new antimicrobials** The GDG 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 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, and not just acquisition cost but the complete cost of care involved with a new medicine (for example, reduced or additional monitoring costs or costs saved from reduced lengths of stay). 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 restricting the prescribing of a new antimicrobial to a specific population may lead to different outcomes of effectiveness and cost effectiveness unless the population is the same as that 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 restriction should be documented and made publicly available. The GDG also concluded that the decision-making body should consider regularly reviewing the restriction to determine if the restriction is still appropriate. **Risk of restriction of prescribing across care settings** 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. 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.
Trade-off between benefits and harms for implementation planning for the introduction of a new antimicrobial	**Implementation planning** The GDG was aware from the call for evidence that there is variability in practice for the planned introduction of a new antimicrobial. Although evidence on effectiveness was limited, 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. 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. 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 not funded as part of the tariff arrangements for payment by results [PbR]). 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. **Laboratory support for prescribing** 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 settings) 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.

The GDG was aware from the experience of its members that prescribing of antimicrobials may sometimes be inappropriate because a laboratory 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 reporting antimicrobial susceptibilities should be in line with:

- national and local treatment guidelines
- the choice of antimicrobial in the local formulary
- the priorities of medicines management 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. The GDG discussed what information prescribers need to ensure the timely adoption and diffusion of a new antimicrobial by planning for implementation. The GDG concluded that organisations should ensure that all prescribers, including those in urgent care services, community nurses and dentists (because 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. The GDG agreed that organisations should signpost prescribers to the following information about a new antimicrobial: • 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. 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 the: • British National Formulary (BNF) • British National Formulary for Children (BNFC) • electronic Medicines Compendium (eMC) • European Medicines Agency (EMA) • Medicines and Healthcare products Regulatory Agency (MHRA).
Trade-off between benefits and harms for the monitoring and evaluation of new antimicrobials	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 recognises as an important aspect of surveillance of a new antimicrobial (see also section 5.6. on antimicrobial resistance surveillance). The GDG agreed that the call for evidence revealed some variation in the

processes organisations have in place for monitoring and surveillance of new antimicrobials 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 developed in the population(s) in which they are being used. This monitoring should also assess the clinical outcomes of treatment (for example, cure and treatment failure rates) with the new antimicrobial. It should ensure that there is reporting of suspected adverse drug reactions that are not the result of medication errors and that these 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
- evaluating local prescribing and resistance patterns
- reviewing clinical outcomes such as cure, treatment failure rates, emerging safety issues, tolerability and length of hospital stay.

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:

- individual prescribing benchmarked against local and national antimicrobial prescribing rates and trends
- local and national antimicrobial resistance rates and trends
- patient safety incidents (related to antimicrobial use, including hospital admissions for potentially avoidable life-threatening infections, infections with *C. difficile* or adverse drug reactions such as anaphylaxis).

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.

8.6 Recommendations and research recommendations

See section 4.1 for a list of all recommendations and appendix F for a summary of the evidence linking the recommendations.

9 References

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10 Glossary

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

Acute otitis media (AOM)

An acute inflammation of the middle ear.

Bacterial isolate

The separation of mixed bacterial strains to single strains for identification.

Febrile morbidity

Any infectious complication following surgery.

In vitro

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

Prophylaxis

Treatment given or action taken to prevent infection.

Spectrum

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

Superinfection

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

Surveillance

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

Ventilator-associated pneumonia

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