Appendix A: Summary of evidence from surveillance

2018 surveillance – [Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use](#) (2015) NICE guideline NG15

Cochrane systematic reviews				
Study	**Related review question/ guideline section**	**Status**	**Key findings**	**Impact on guideline recommendations**
Schuetz P, Wirz Y, Sager R et al. (2017) Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections(1)	6.2 What interventions, systems and processes are effective and cost effective in changing health and social care practitioners' decision-making to ensure appropriate antimicrobial stewardship?	Updates a Cochrane review from 2013 which was included in the original guideline.	The review found 32 randomised controlled trials (RCTs) including 18 new trials for the 2017 update, and individual participant data were obtained from 26 trials (n=6,708). Procalcitonin to guide initiation and duration of antibiotic treatment resulted in lower risks of mortality, lower antibiotic consumption, and lower risk for antibiotic-related side effects. Results were similar for different clinical settings and types of acute respiratory infections.	The conclusion of the updated review is similar to the conclusion of the original review which was considered by NG15. Therefore the evidence is unlikely to impact NG15. Procalcitonin was discussed by the guideline committee (see [NG15 full guideline](#)) who agreed with the conclusion in the [full version of the NICE Pneumonia guideline](#) (CG191) that 'C-reactive protein was considered to be cheaper than procalcitonin and more clinically useful' which resulted in a recommendation in CG191 to consider a point of care C-reactive protein test. NG15 links to CG191 in recommendation 1.1.30 'Consider point‑of‑care testing in primary care for patients with suspected lower respiratory tract infections as described in the NICE guideline on pneumonia.'

Tonkin-Crine SK, Tan PS, van Hecke O et al. (2017) Clinician-targeted interventions to influence antibiotic prescribing behaviour for acute respiratory infections in primary care: an overview of systematic reviews(2)	6.2 What interventions, systems and processes are effective and cost effective in changing health and social care practitioners' decision-making to ensure appropriate antimicrobial stewardship? 7.2 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?	First published in 2017 therefore not considered by NG15.	This review of 8 reviews (5 Cochrane Reviews [33 included trials] and 3 non-Cochrane reviews [11 included trials]) found that shared decision making, C-reactive protein testing, and procalcitonin-guided management reduced antibiotic prescribing for patients with acute respiratory infections in primary care.	Shared decision making is already recommended by NG15 recommendation 1.1.31 'Prescribers should take time to discuss with the patient and/or their family members or carers (as appropriate)…' so the Cochrane review agrees with the guideline. Procalcitonin and C-reactive protein were discussed by the guideline committee (see NG15 full guideline) who agreed with the conclusion in the full version of the NICE Pneumonia guideline (CG191) that 'C-reactive protein was considered to be cheaper than procalcitonin and more clinically useful' which resulted in a recommendation in CG191 to consider a point of care C-reactive protein test. NG15 links to CG191 in recommendation 1.1.30 'Consider point‑of‑care testing in primary care for patients with suspected lower respiratory tract infections as described in the NICE guideline on pneumonia.'

Spurling GK, Del Mar CB, Dooley L et al. (2017) Delayed antibiotic prescriptions for respiratory infections(3)	6.2 What interventions, systems and processes are effective and cost effective in changing health and social care practitioners' decision-making to ensure appropriate antimicrobial stewardship?	Updates a Cochrane review from 2013 which was included in the original guideline.	The review added 1 new RCT (n=405). Overall, it included 11 studies (n=3,555). Delayed antibiotics resulted in a significant reduction in antibiotic use compared to immediate antibiotics prescription.	NG15 already recommends that where immediate prescribing is not the most appropriate option, delayed antibiotics should be discussed as an option for patients. No impact is expected.
Davey P, Marwick CA, Scott CL (2017) Interventions to improve antibiotic prescribing practices for hospital inpatients(4)	5.2 What interventions, systems and processes are effective and cost effective in reducing antimicrobial resistance without causing harm to patients?	Updates a Cochrane review from 2013 which was included in the original guideline.	The 2013 review included 89 studies. The 2017 review of 221 studies (58 RCTs, and 163 non-RCTs) examined interventions that fell broadly into 2 categories: restrictive techniques (rules to make physicians prescribe properly), and enablement techniques (advice or feedback to help physicians prescribe properly). There was high-certainty evidence that interventions increased compliance with antibiotic policy and reduced duration of antibiotic treatment. Lower use of antibiotics probably does not increase mortality and likely reduces length of stay. Enablement consistently increased the effect of interventions, including those with a restrictive component, and feedback further increased intervention effect.	NG15 already recommends restrictive and enablement techniques to improve antibiotic stewardship. No impact is expected.

O'Sullivan JW, Harvey RT, Glasziou PP (2016) Written information for patients (or parents of child patients) to reduce the use of antibiotics for acute upper respiratory tract infections in primary care(5)	5.2 What interventions, systems and processes are effective and cost effective in reducing antimicrobial resistance without causing harm to patients?	First published in 2016 therefore not considered by NG15.	This review of 2 RCTs (both at high-risk of bias; n=827 children with acute upper respiratory tract infections; 558 from 61 general practices in England and Wales; and 269 from primary care doctors in the USA) found moderate quality evidence from 1 study that, versus usual care, trained GPs providing written information to parents can reduce the number of antibiotics used by patients without any negative impact on reconsultation rates or parental satisfaction with consultation. Versus usual care, low quality evidence from 2 studies showed that providing written information reduced antibiotic prescribing, but low quality evidence also showed that when doctors were also given feedback on their antibiotic prescribing along with providing written information to parents, antibiotic prescribing increased.	NG15 recommendation 1.1.31 states 'Prescribers should take time to discuss with the patient and/or their family members or carers (as appropriate)… whether they need any written information about their medicines and any possible outcomes.' so the Cochrane review broadly agrees with the guideline. As the evidence is from 2 trials of moderate/low quality with high risk of bias, no impact is anticipated.

Coxeter P, Del Mar CB, McGregor L (2015) Interventions to facilitate shared decision making to address antibiotic use for acute respiratory infections in primary care(6)	7.2 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?	First published in 2015 therefore not considered by NG15.	This review examined 10 published reports of 9 original RCTs in over 1,100 primary care doctors and around 492,000 patients. There is moderate quality evidence that interventions to facilitate shared decision making reduced antibiotic use for acute respiratory infections in primary care (immediately after or within 6 weeks of the consultation), compared with usual care. Reduction in antibiotic prescribing occurred without an increase in patient-initiated re-consultations or a decrease in patient satisfaction with the consultation. Effects on longer-term rates of prescribing are uncertain.	NG15 recommendation 1.1.31 already encourages shared decision making and states 'Prescribers should take time to discuss with the patient and/or their family members or carers (as appropriate)…' so no impact is expected on the guideline.

Policy and guidance				
Document	**Related review question**	**Status**	**Details**	**Impact on guideline recommendations**
Antimicrobial resistance: resource handbook, Public Health England 2016 (updated with new version of handbook 2017)(7)	No specific related review question.	Updated April 2017	This handbook is a collation of national antimicrobial resistance, antimicrobial stewardship and infection prevention and control resources which are relevant for an array of care settings. The handbook includes supporting materials relating to: - strategy and national guidance - policy and recommendations - education and training - guidance and tools - surveillance - international resources	This document links out to an array of other documents (some of which are discussed below) and as such does not directly impact NG15. This resource will be highlighted to the relevant NICE system engagement teams for consideration.

[Progress report on the UK 5 year AMR strategy 2015](), Department of Health, 2016(8)	No specific related review question.	Published 2016	The first progress report for 2014 was referred to in the full version of NG15. The second annual progress report describes what was achieved in the second year of implementation, including a number of significant achievements on the international stage. The UK 5 year antimicrobial resistance (AMR) strategy 2013 to 2018 represents an ambitious programme to slow the development and spread of AMR taking a "One-Health" approach spanning people, animals, agriculture and the wider environment. This is published on behalf of the high level steering group responsible for driving delivery of the UK AMR strategy. This progress report notes 'Other activity in support of improved prescribing of antibiotics includes the NICE guidance on Medicines Optimisation in March and on Antimicrobial Stewardship (i.e. NG15) in August 2015.' The report notes 7 key action areas: 1. Improving Infection Prevention and Control (IPC) practices in human and animal health 2. Optimising prescribing practice 3. Improved education, training and public engagement 4. Developing new drugs, treatments and diagnostics 5. Better access to and use of surveillance in human and animal sectors	Action areas 1, 4, 6 and 7 are out of scope of NG15. Action areas 2, 3 and 5 are aligned with NG15. No impact is expected.

			6. Better identification and prioritisation of AMR research	
			7. Strengthened international collaboration working	
[Global action plan on antimicrobial resistance](#). World Health Organization, 2015(9)	No specific related review question.	Published 2015	The May 2015 World Health Assembly adopted a global action plan on antimicrobial resistance, which outlines 5 objectives:	Objectives 3 and 5 are out of scope of NG15. NG15 is broadly aligned with the other objectives, particularly objective 4 which states that Member States should 'Develop and implement comprehensive action plans on antimicrobial resistance that incorporate the following elements: […] provision of stewardship programmes that monitor and promote optimisation of antimicrobial use at national and local levels in accordance with international standards in order to ensure the correct choice of medicine at the right dose on the basis of evidence.' No impact is expected.
			1. to improve awareness and understanding of antimicrobial resistance through effective communication, education and training;	
			2. to strengthen the knowledge and evidence base through surveillance and research;	
			3. to reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures;	
			4. to optimise the use of antimicrobial medicines in human and animal health; and	
			5. to develop the economic case for sustainable investment that takes account of the needs of all countries and to increase investment in new medicines, diagnostic tools, vaccines and other interventions.	

| Antibacterial agents in clinical development: analysis of the antibacterial clinical development pipeline, including tuberculosis, World Health Organization 2017(10) | No specific related review question. | Published 2017 | WHO reviewed the publically available information on the current clinical development pipeline of antibacterial agents to assess the extent to which the drug candidates act against priority pathogens, Mycobacterium tuberculosis, and Clostridium difficile.

The report states that 'New antibiotics alone will not be sufficient to mitigate the threat of antimicrobial resistance. Their development should go hand in hand with infection prevention and control activities and fostering of appropriate use of existing and future antibiotics through stewardship measures.' | The scope of NG15 excludes research for new antimicrobials therefore this report is unlikely to affect the guideline.

NG15 is aligned with the statement about the need for stewardship measures. |

| English surveillance programme for antimicrobial utilisation and resistance (ESPAUR), Public Health England, 2014 (updated annually – 2016 and 2017 reports now available)(11) | No specific related review question. | Updated 2016 and 2017 | 2016 report:

The 2016 report makes a number of recommendations. None of these are directly targeted at NICE.

However NICE is mentioned in the recommendations in a number of places:

• 'Public Health England staff should ensure they are able to direct organisations and individuals to the resources for antimicrobial stewardship (AMS) guidance available for primary care and secondary care from NICE […] including […] the NICE Antimicrobial Stewardship Guidance.'
• 'Directors of public health should support the development of local AMS collaboratives in line with NICE Antimicrobial Stewardship Guidance (NG15).'
• 'All healthcare organisations (both community and hospital) should perform a self-assessment of their organisation's antimicrobial stewardship practice against the NICE Antimicrobial Stewardship Guidance (NG15), and use the toolkit to develop an organisation focussed action plan.'

The report also notes that the 2016 Foundation Doctors curricula for the first time include antimicrobial resistance (AMR) as part of the training outcomes descriptors: | The 2016 report makes no recommendations directly targeted at NICE, but recommends implementing NG15, and notes that the 2016 Foundation Doctors curricula includes antimicrobial resistance in line with recommendations in NG15 on education and training. Overall, the report aligns with NG15. No impact is expected.

Similarly, no impact is expected with the 2017 report. |

				• 'Prescribes and administers oxygen, fluids and antimicrobials as appropriate eg in accordance with NICE guidance on antimicrobial stewardship and sepsis' The report also has a specific section about NICE: 'NICE continues to provide guidance and advice to support the wider AMS including a new programme of work to develop a suite of prescribing guidelines for the management of common infections in primary and secondary care. These guidelines will primarily be aimed at prescribers but will be valuable to other health professionals and commissioners. In support of this work, the BNF section on antimicrobials will be reviewed to include links to information about regional resistance levels. 'In addition to the NICE guideline on AMS systems for effective antimicrobial use (NG15), NICE is currently developing a complementary guideline: AMS changing risk-related behaviours in the general population. To further improve effective antimicrobial stewardship a quality standard (QS121) was published in April 2016, which aims to reduce the emergence of AMR (loss of effectiveness of antimicrobials). 'The NICE Key Therapeutic Topics work includes AMS as a topic. Prescribing data from the comparators developed by NHS Digital are also included to allow organisations to benchmark and assess the degree of variation in key areas of AMR.'	

				2017 report:
				The report has a specific section about NICE. Key points are that:
				• NICE is working with Public Health England on antimicrobial prescribing guidelines. The first 3 topics are planned to publish in the 2017/18 business year with sinusitis (acute) due for publication in October 2017
				• In January 2017, NICE published a guideline Antimicrobial stewardship (AMS): changing risk-related behaviours in the general population (NG63), complementary to the NICE guideline on Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (NG15)
				• NICE is also developing Antimicrobial Prescribing Advice to support the appropriate use and stewardship of new antimicrobials. The first advice is on Ceftazidime-avibactam (Zavicefta) and is due to be published in October 2017.
				• NICE's current Medtech innovation briefings are developed to support the use of innovative medical devices, diagnostics and digital technologies, including those that relate to the antimicrobial stewardship agenda. Over the past year, MIBs were published on FebriDx for C-reactive protein and Myxovirus resistance protein A testing in primary care (July 2017), eazyplex SuperBug kits for detecting carbapenemase-producing organisms (Feb 2017), QuikRead go for C-reactive protein testing in primary care (Sept 2016) and Alere

			Afinion CRP for C-reactive protein testing in primary care (Sept 2016).	
			• NICE is also collaborating with the Department of Health (DH) on a research project exploring the assessment of new antimicrobials with high potential to address unmet need.	
			• The NICE Key Therapeutic Topics work includes Antimicrobial Stewardship as a topic	

UK one health report: antibiotics use in humans and animals, Public Health England & Veterinary Medicines Directorate, 2015(12)	No specific related review question.	Published 2015	Joint report on human and animal antibiotic use, sales and resistance in the UK in 2013	Recommendations 4, 6, 7, 8 and 10 are out of scope of NG15.
			The report makes 10 recommendations:	Recommendations 1, 2, 3, 5 and 9 are broadly aligned with NG15.
			1. All Salmonella species are sent to the relevant reference laboratories for speciation and antimicrobial susceptibility testing.	The report is unlikely to affect NG15.
			2. Development of a national sentinel surveillance system for Campylobacter.	
			3. A single standardised nationally agreed methodology for routine antibiotic testing.	
			4. Develop guidance related to recommended antibiotic and bacterial combinations.	
			5. Harmonised monitoring of antimicrobial resistance in Salmonella and Campylobacter.	
			6. Explore data available on human sales of antibiotics.	
			7. Veterinary Medicines Directorate (VMD) will conduct carbapenem resistance monitoring.	
			8. VMD will collect farm level data from the pig sector; and collect antibiotic consumption data at an individual farm level.	
			9. Activities should be enhanced through engagement with the European Antibiotic Awareness Day campaign and aligning training programmes for human and animal health professionals.	
			10. Produce a further report in 2 years on the burden of antimicrobial resistance in imported food animals.	

Tackling drug-resistant infections globally: final report and recommendations, Review on Antimicrobial Resistance (O'Neill Review Team), 2016(13)	No specific related review question.	Published 2016	The final report from the Review on Antimicrobial Resistance. Following 19 months of consultation and 8 interim papers, this report sets out the Review on Antimicrobial Resistance's final recommendations to tackle antimicrobial resistance. The report makes 10 main recommendations: 1. A massive global public awareness campaign 2. Improve hygiene and prevent the spread of infection 3. Reduce unnecessary use of antimicrobials in agriculture and their dissemination into the environment 4. Improve global surveillance of drug resistance in humans and animals 5. Promote new, rapid diagnostics to cut unnecessary use of antibiotics 6. Promote the development and use of vaccines and alternatives 7. Improve the numbers, pay and recognition of people working in infectious disease 8. Establish a Global Innovation Fund for early-stage and non-commercial research 9. Better incentives to promote investment for new drugs and improving existing ones 10. Build a global coalition for real action – via the G20 and the United Nations	Recommendations 1, 2, 3, 6, 7, 8, 9 and 10 are out of scope of NG15. Recommendations 4 and 5 are broadly aligned with NG15. The report is unlikely to affect NG15.

[Government response to the Review on antimicrobial Resistance](#), Department of Health, September 2016(14)	No specific related review question.	Published 2016	Government response to the above report. NICE is mentioned in relation to recommendation 5 of the above report: 'The Government is already working to promote point of care diagnostics as a key project in the UK antimicrobial resistance implementation plan, but recognises that a step change is necessary to accelerate this work. We will therefore work with relevant bodies, including Public Health England, NHS Improvement, NHS England and the National Institute for Health and Care Excellence (NICE), in 2016/17 to explore the feasibility of assessing the effectiveness of existing diagnostics'	There is no direct implication for NG15 and no impact is expected.
[Antimicrobial resistance local indicators](#), Public Health England(15)	No specific related review question.	Last updated to add new indicators in October 2017	Local antimicrobial resistance data covering England which is refine-able and searchable. Antimicrobial resistance local indicators are publically available data intended to raise awareness of antibiotic prescribing; and to facilitate the development of local action plans. The data published in this tool may be used by healthcare staff, commissioners, directors of public health, academics and the public to compare the situation in their local area to the national picture.	A link to this tool will be added to NG15.

NIHR Signals

Document	Related review question	Status	Details	Impact on guideline recommendations
Carefully managed antibiotic use could halve antibiotic-resistant infections(16) Based on: Baur D, Gladstone BP, Burkert F, et al. (2017) Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and *Clostridium difficile* infection: a meta-analysis. Lancet Infect Dis.(17)	No specific related review question.	Published October 2017	Stewardship programmes appear to halve the incidence of multi-drug resistant gram-negative bacteria, reduce the incidence of extended spectrum beta-lactamase producing gram-negative bacteria such as Escherichia coli and Clostridium difficile, and may reduce overall antibiotic resistance.	This review is aligned with NG15 in that commissioners should establish antibiotic stewardship programmes in hospitals and primary care.

Education targeted at both parents and GPs reduces antibiotic prescribing for children (18) Based on: Hu Y, Walley J, Chou R, et al. (2016) Interventions to reduce childhood antibiotic prescribing for upper respiratory infections: meta-analysis. J Epidemiol Community Health (19)	5.2 What interventions, systems and processes are effective and cost effective in reducing antimicrobial resistance without causing harm to patients?	Published August 2016	The interventions examined included a training session, prescribing feedback for clinicians, and leaflets and posters for parents. Interventions were associated with lower rates of antibiotic prescribing when compared to usual care.	The evidence is aligned with NG15 which already recommends training and feedback for prescribers, and information for patients.

Shared decision making in primary care can reduce antibiotic prescribing (20)

Based on: Coxeter P, Del Mar CB, McGregor L, et al. (2015) Interventions to facilitate shared decision making to address antibiotic use for acute respiratory infections in primary care. Cochrane Database Syst Rev (6) | 7.2 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? | Published January 2016 | This Signal is based on the Cochrane review by Coxeter et al. 2015, which is discussed in the table of Cochrane reviews above. | No impact on NG15 is expected. |

Editorial and factual amendments

During surveillance of the guideline we identified the following issues that should be amended:

- In the box at the start of section 1 of the NICE version 'Recommendations', the following sentence will be added: 'This guideline should be read in conjunction with NICE's guideline on antimicrobial stewardship: changing risk-related behaviours in the general population and NICE guidance on managing common infections'.
- In recommendation 1.2.12, the hyperlinks to the British National Formulary (BNF) and British National Formulary for Children (BNFC) are broken and need correcting [correct pages here and here respectively]
- In section 2 of the NICE version 'Implementation: getting started':
  - The hyperlink to the TARGET toolkit is broken in 2 places and will be fixed [correct page now here]
  - A link will be added to the following resource: Antimicrobial resistance local indicators (Public Health England)

References

1. Schuetz P, Wirz Y, Sager R, Christ-Crain M, Stolz D, Tamm M, et al. (2017 [cited 2017 Nov 16]) Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Cochrane Database of Systematic Reviews

2. Tonkin-Crine SK, Tan PS, van Hecke O, Wang K, Roberts NW, McCullough A, et al. (2017 [cited 2017 Nov 16]) Clinician-targeted interventions to influence antibiotic prescribing behaviour for acute respiratory infections in primary care: an overview of systematic reviews. Cochrane Database of Systematic Reviews

3. Spurling GK, Del Mar CB, Dooley L, Foxlee R, Farley R (2017 [cited 2017 Nov 20]) Delayed antibiotic prescriptions for respiratory infections. Cochrane Database of Systematic Reviews

4. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, et al. (2017 [cited 2017 Nov 20]) Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database of Systematic Reviews

5. O'Sullivan JW, Harvey RT, Glasziou PP, McCullough A (2016 [cited 2017 Nov 20]) Written information for patients (or parents of child patients) to reduce the use of antibiotics for acute upper respiratory tract infections in primary care. Chichester, UK: John Wiley & Sons, Ltd

6. Coxeter P, Del Mar CB, McGregor L, Beller EM, Hoffmann TC (2015 [cited 2017 Nov 20]) Interventions to facilitate shared decision making to address antibiotic use for acute respiratory infections in primary care. Cochrane Database of Systematic Reviews

7.   Public Health England (2017 [cited 2017 Nov 20]) Antimicrobial Resistance: resource handbook [Internet].

8.   Department of Health (2016 [cited 2017 Dec 1]) Progress report on the UK 5 year AMR strategy: 2015 [Internet].

9.   World Health Organization (2015 [cited 2017 Dec 1]) Global action plan on antimicrobial resistance [Internet]. World Health Organization

10.   World Health Organization (2017 [cited 2017 Dec 1]) Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline, including Mycobacterium tuberculosis [Internet]. World Health Organization

11.   Public Health England (2017 [cited 2017 Dec 1]) English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report [Internet].

12.   Public Health England and Veterinary Medicines Directorate (2015 [cited 2017 Dec 1]) UK one health report: antibiotics use in humans and animals [Internet].

13.   O'Neill J (2016) Tackling drug-resistant infections globally: final report and recommendations.

14.   Department of Health (2016 [cited 2017 Dec 1]) Antimicrobial resistance review: government response [Internet].

15.   Public Health England ([cited 2017 Dec 1]) Antimicrobial resistance local indicators [Internet].

16.   NIHR (2017 [cited 2017 Dec 1]) Carefully managed antibiotic use could halve antibiotic-resistant infections.

17.   Baur D, Gladstone BP, Burkert F, Carrara E, Foschi F, Döbele S, et al. (2017 [cited 2017 Dec 1]) Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and Clostridium difficile infection: a systematic review and meta-analysis. The Lancet. Infectious diseases 17(9):990–1001

18.   NIHR (2016 [cited 2017 Dec 1]) Education targeted at both parents and GPs reduces antibiotic prescribing for children.

19.   Hu Y, Walley J, Chou R, Tucker JD, Harwell JI, Wu X, et al. (2016 [cited 2017 Dec 1]) Interventions to reduce childhood antibiotic prescribing for upper respiratory infections: systematic review and meta-analysis. Journal of epidemiology and community health 70(12):1162–70

20.   NIHR (2016) Shared decision making in primary care can reduce antibiotic prescribing.