Managing Common Infections

Acute cough (including acute bronchitis): antimicrobial prescribing

Stakeholder comments table

23/08/2018 – 20/09/2018

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National Minor Illness Centre	Guideline	16-18	general	It is very unusual for NICE guidance to make positive recommendations based on such a low quality of evidence. If there was an underlying reason for this change in practice, please could this be made explicit? This issue aside, it will not be possible to give evidence-based recommendations for the OTC products because the dosages used in the trials are much higher than those which are available OTC: dextromethorphan 30mg/dose (15 mg in Benylin Dry Cough) and guaifenesin 1200 mg/24hr (800mg /24hr in Benylin Mucous Cough). We wondered why you did not consider the evidence for vapour rub (camphor, menthol and eucalyptus), which would give an OTC option for coughing children whose parents cannot sleep: Paul IM, Beiler JS, King TS, Clapp ER, Vallati J, Berlin CM. Vapor rub, petrolatum, and no treatment for children with nocturnal cough and cold symptoms. Pediatrics. 2010 Nov 2:peds-2010. (http://pediatrics.aappublications.org/content/126/6/1092)	Thank you for your comment. This was discussed by the committee and the recommendations on self-care have been amended to reflect the strength of the evidence. The committee considered the high doses of over the counter medicines used in some of the trials. However agreed, based on their experience that some people may wish to try guaifenesin or antitussives (apart from codeine) for the relief of cough symptoms. Considering the limited evidence for dextromethorphan (which is for a single high dose) and an association with adverse effects, the committee agreed to amend the recommendations to remove specific reference to dextromethorphan. For non-antimicrobial and non-pharmacological interventions, preparations were grouped into classes based on the Cochrane review of over-the-counter preparations (Smith et al. 2014) and other included systematic reviews. The review protocol has been updated to include details

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					on this. These classes were then used by the committee to make decisions on whether to progress down the hierarchy of evidence (from systematic reviews, to RCTs, or further) if there was insufficient evidence; and to limit interventions only to those commonly in use in the UK. For over-the-counter (OTC) preparations, classes were OTC expectorants, OTC antitussives, OTC antihistamines and decongestants, and OTC mucolytics. The committee agreed that for these interventions, the systematic review by Smith et al. 2014 provided sufficient evidence, and progressing to RCT evidence was not required. The committee also agreed that the systematic review included all commonly used OTC preparations and there was no requirement to look further than this for evidence on OTC preparations not included in this review (such as vapour rub). The reference provided (Paul et al. 2010) was therefore not included.
National Minor Illness Centre	Evidence review	32	36 and 44	Given the lack of any RCT comparing the effectiveness of different antibiotics, the rationale for changing the first line antibiotic in adults from amoxicillin to doxycycline does not seem compelling. The subgroup analyses show (for three old trials of doxycycline vs placebo): no significant difference in clinical improvement; a reduction of 0.6 illness days; and a reduction of cough at follow-	Thank you for your comment. This was discussed by the committee, however the recommended antibiotic choices have not been amended. The committee were aware of the limited evidence to indicate the benefit of doxycycline over amoxicillin. However, they agreed that amoxicillin should be reserved, when possible, for use in more serious infections where bacterial infection is more common, for example pneumonia. This is

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				up visit (NNT of 6). Similar analyses for amoxicillin were not available. Doxycycline carries the hazard of inadvertent prescription to a woman who does not realise that she is pregnant. It also, in our experience, has a worse side effect profile than amoxicillin. The concern about amoxicillin-resistant E. Coli is, in our opinion, misplaced; given that the resistance rate is already above 50%, it is not good practice to use amoxicillin for the blind treatment of a UTI.	because of concerns that amoxicillin drives resistance not just in pneumococci but also in gram negative organisms. The committee was aware of evidence that the risk of resistance to amoxicillin is significantly increased in urinary isolates of *Escherichia coli* following a course of amoxicillin. A systematic review and meta-analysis of observational studies and randomised controlled trials (Costelloe et al. 2010) found that people prescribed an antibiotic, including amoxicillin, for a respiratory tract infection (not just a urinary tract infection) are more likely to develop resistance to that antibiotic in respiratory and urinary tract bacteria. These effects are greatest in the first month after use, but are detectable for up to 12 months. There is a concern that using amoxicillin in conditions such as acute cough or sore throat, where the benefits of antibiotics are marginal, drives resistance without adding benefit. The committee did agree that as the evidence of benefit of doxycycline over amoxicillin, clarithromycin or erythromycin is limited, these antibiotics should be offered as alternative first choices, rather than second-line. This also reflects safety issues regarding use of doxycycline in women who are not aware they are pregnant. The footnote to explain the safety warning on doxycycline has been amended to include women of child bearing age.
Royal College of Physicians and Surgeons of Glasgow	guideline	general		The Royal College of Physicians and Surgeons of Glasgow although based in Glasgow represents Fellows and Members throughout the United Kingdom who practice in the field of	Thank you for your comment.

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				Bronchiectasis. While NICE has a remit for England, many of the recommendations are applicable to all devolved nations including Scotland. They should be considered by the relevant Ministers of the devolved governments. The College welcomes this review of acute cough including acute bronchitis by NICE. It is keenly interested in reducing the prescriptions for antibiotics. This should promote reduction in antibiotic resistance as well as reduction in costs. It recognises the importance of working with patients to manage their own disease.	
Royal College of Physicians and Surgeons of Glasgow	guideline	general		Our expert reviewer felt this is an important and timely guideline. Although the evidence does suggest some possible benefits of treatment of acute cough with antibiotics and inhaled corticosteroids, these are minor at best and, as highlighted in the report, it would send the wrong message that prescribed treatment is needed for a largely self-limiting condition. Situations where antibiotics might be considered in higher risk individuals are clearly set out. While the guidelines set out when patients with cough and other (such as systemic) symptoms should be referred on for investigation, this needs further explanation and amplification in the guideline given the public campaign to seek help if a cough lasts longer than	Thank you for your comments. The population covered in this guideline includes people with acute cough (commonly defined as a cough that lasts less than 3 weeks). The committee was unable to make recommendations on people who should be referred for investigation who have a cough which lasts longer than 3 weeks. However, the recommendation to refer people with an acute cough to hospital, or seek specialist advice on further investigation and management, if they have any symptoms or signs suggesting a more serious illness or condition (for example sepsis, a pulmonary embolism or lung cancer), would cover this.

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				three weeks This guideline deals with cough up to three weeks. There will inevitably be an overlap.	
British Society for Antimicrobial Chemotherapy (BSAC)	Guideline	3	18	*1.1.7 Do not offer an antibiotic to people for an acute cough associated with an upper respiratory tract infection who are not systemically very unwell or at higher risk of complications* This is difficult to apply without some standardisation of 'very unwell'. The 'higher risk of complications' clause could be hyperlinked to 1.1.14 Some people regard bronchitis as URTI: they are wrong, but to those people this will read confusingly when they reach the next section which is about acute bronchitis. It might help to clarify the meaning of URTI, eg '*Do not offer an antibiotic to people for an acute cough associated with a predominantly upper respiratory tract infection (eg laryngitis or tracheitis) who are not systemically very unwell or at higher risk of complications'*	Thank you for your comments. Based on the evidence identified, the committee were unable to provide a definitive list of people in whom it may be appropriate to prescribe an antibiotic. Therefore, the term 'systemically very unwell' was used, to allow clinical judgement to be used in individual circumstances when deciding if an antibiotic may be appropriate. 'Systemically very unwell' is a term used in the NICE guideline on respiratory tract infections (self-limiting): prescribing antibiotics, and it is assumed that clinicians will use clinical judgement when applying this. Under the section, identifying those patients with respiratory tract infections who are likely to be at risk of developing complications, there is a recommendation to offer an immediate antibiotic and/or further appropriate investigation and management if the patient is systemically very unwell. A link has been added to the term 'higher risk of complications' to link to the recommendation describing those at higher risk of complications. The definition of acute bronchitis in the terms used in the guideline has been amended to state that this is a lower respiratory tract infection. The recommendation has not been amended to clarify the meaning of upper respiratory tract infection, as this is believed to be clear from the definitions included.

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British Society for Antimicrobial Chemotherapy (BSAC)	Guideline	4	1	*1.1.10 For adults with an acute cough associated with acute bronchitis who have had a point of care C-reactive protein test, follow the NICE guideline on pneumonia in adults: diagnosis and management.* This will confuse people. The NICE guideline on pneumonia does include a section about CRP testing in patients who don't have pneumonia, but arguably it's in the wrong place. Might be better just to replicate that section in the acute cough guideline rather than refer the reader to somewhere else that on the face of it doesn't look relevant.	Thank you for your comments. The committee understood the limitations with redirecting to the NICE guideline on pneumonia. However, they agreed it was important to have the recommendations on C-reactive protein accessible from the antimicrobial prescribing guideline on acute cough. For editorial reasons, recommendations cannot be replicated in the NICE guideline on pneumonia and the antimicrobial prescribing guideline on acute cough, therefore the link to the NICE guideline on pneumonia has been retained. However, this will be clearer in the NICE pathway.
British Society for Antimicrobial Chemotherapy (BSAC)	Guideline	general	general	NICE CG101 (Chronic obstructive pulmonary disease in over 16s: diagnosis and management) gives advice on the management of infective exacerbations of COPD, which in pathological terms must be assumed to be bronchitis. In this group the advice is that antibiotics should be used to treat exacerbations of COPD associated with a history of more purulent sputum, and that exacerbations without more purulent sputum do not need antibiotic therapy (unless they have pneumonia). This creates a conflict between two guidelines – the acute cough guideline that recommends antibiotics to a patient with a cough and a comorbidity such as COPD that confers a higher risk of complications, and the COPD guideline	Thank you for your comments. This guideline does not cover treating cough associated with acute exacerbations of chronic obstructive pulmonary disease (COPD). In the overview section of the guideline, readers are directed to the NICE antimicrobial prescribing guideline on 'acute exacerbation of COPD' for treating cough associated with acute exacerbations of COPD, as well to the NICE guideline on 'COPD in over 16s: diagnosis and management'.

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				that interposes the 'more purulent sputum' threshold. I think this should be clarified, either by excluding exacerbation COPD from the acute cough guideline or (better) by including the 'more purulent sputum' requirement in the acute bronchitis section of the cough guideline.	
British Society for Antimicrobial Chemotherapy (BSAC)	Guideline	general	general	I cannot see anything that suggests reviewing previous, recent sputum microbiology before prescribing (e.g. within last 12 months) when available. This is likely to be more important in higher risk patients who are more likely to have had sputum sent previously. If for example a patient had Haemophilus in their sputum 4 months prior, resistant to doxycycline, but sensitive to amoxicillin, then one should account for that when that information is available. Not to do so will potentially lead to two or more courses of antibiotics rather than just one.	Thank you for your comments. This was discussed further by the committee, however no amendments were made to include reviewing previous sputum microbiology as the committee agreed that it would be unlikely that most people with acute cough would have recent sputum samples available, and testing should not be encouraged.
Royal College of General Practitioners	Guideline	General	General	Question 1: The newly recommended choice and length of antibiotics will have the biggest impact on practice. It should not be too challenging to implement provided the information is disseminated to primary care effectively. Doxycycline is usually given as a 7 day course. Will these guidelines be in line with Public Health England guidelines for antibiotics? Can NICE and PHE publish joint guidelines regularly to avoid any confusion in primary care.	Thank you for your comment. NICE is aware of the important role played by Public Health England guidance on the treatment of acute cough. We have worked closely with Public Health England to produce this guideline, and this guideline will replace the Public Health England antibiotic choice recommendations for acute cough. A summary table of all NICE and Public Health England guidance has also recently been published, which will be updated regularly. The BNF receive all NICE antimicrobial prescribing guidelines once they

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				Will the BNF app be adjusted?	are published and processes are in place to ensure appropriate amendments are made.
Royal College of General Practitioners	Guideline	General	General	Question 2: Implementation of the draft guidelines should not lead to any significant increase in costs, if anything there is a potential for resource savings with a reduction in prescriptions issued.	Thank you for your comment.
Royal College of General Practitioners	Guideline	General	General	Question 3: All users would be helped by clear and consistent national guidance for the public, pharmacists and general practitioners regarding self-care of acute coughs and the treatments that have and do not have any evidence to support their use in the management of acute coughs.	Thank you for your comment.
Royal College of General Practitioners	Guideline	General	General	Question 4: The changes in antibiotic type and length of treatment is a significant change to practice but it is possible to achieve if the information is disseminated effectively. A wide variety of other treatments and self-care options have been reviewed and had their evidence assessed by this guideline. The quality of the evidence and the wide number of options reviewed may have a negative impact on the uptake of this part of the guidelines and to help prevent this it is important that clear, consistent and concise guidance is disseminated. The key issues and learning points for professional groups is the new guidance on antibiotic prescribing and the evidence for other treatment options and self-care advice.	Thank you for your comments. The most commonly used interventions were prioritised by the committee and included in the evidence review. The committee were also aware of the low quality of the evidence available and have attempted to provide clear guidance based on the evidence and their own experience.
Royal College of General Practitioners	Draft guideline	general		There is no cross reference to NG 12 suspected cancer concerning lung cancer in those aged over 40 years e.g.	Thank you for your comment. The recommendations suggest that specialist advice or referral should be sought when

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				cough and smoking suggest the need for an urgent CXR according to the guideline.	there are symptoms or signs suggesting a more serious illness or condition, including lung cancer. However, there are a large number of conditions which may be suspected, and links cannot practically be included for them all.
Royal College of General Practitioners	Draft guideline	3	15	There is no definition of "systemically very unwell" Much clearer guidance is needed on clinical features that define the patient group who need an immediate antibiotic. Currently all the guideline says is people who are identified as systemically very unwell or in groups at high risk of complications which is not at all clear enough. It can frustrating and demoralising to hear constant criticism that GPs overprescribe and prescribe inappropriately when actually no guidance can give any clear answer on which signs/symptoms predict that an immediate antibiotic is needed. Whilst it is challenging to clarify which signs/symptoms are useful in defining patient groups who need immediate antibiotics, Clinicians need a clear analysis of the evidence of the combination of clinical signs of symptoms that predict that someone needs an immediate antibiotic e.g. fever lasting more than 5 days, pulse / BP, crackles in the chest, loss of appetite, severe lethargy, NEWS2 Score etc.	Thank you for your comment. Based on the evidence identified, the committee were unable to provide a definitive list of people in whom it may be appropriate to prescribe an antibiotic. Therefore, the term 'systemically very unwell' was used, to allow clinical judgement to be used in individual circumstances when deciding if an antibiotic may be appropriate. 'Systemically very unwell' is a term used in the NICE guideline on respiratory tract infections (self-limiting): prescribing antibiotics, and it is assumed that clinicians will use clinical judgement when applying this. Under the section, identifying those patients with respiratory tract infections who are likely to be at risk of developing complications, there is a recommendation to offer an immediate antibiotic and/or further appropriate investigation and management if the patient: - is systemically very unwell - has symptoms and signs suggestive of serious illness and/or complications - is at high risk of serious complications because of pre-existing comorbidity - is older than 65/80 years with acute cough and two/one or more of the following criteria: hospitalisation in previous year, type 1 or type

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				The guideline must very clearly state that there is a lack of good evidence on clinical features of cough to help clinicians target appropriate antibiotic usage, and that more research is urgently needed on this. All studies are at risk of suffering from recruitment bias as very often there is no clear description of the clinical groups excluded from the trial (those too unwell, who need an immediate antibiotic)	2 diabetes, history of congestive heart failure, current use of oral glucocorticoids. In order to make these recommendations, the committee for the NICE guideline on respiratory tract infections (self-limiting): prescribing antibiotics considered observational data to identify people with respiratory tract infections who were more likely to be at risk of developing complications. Such prognostic studies were outside the scope of this antimicrobial prescribing guideline, and no evidence was identified from the included RCTs and systematic reviews to suggest who will benefit most from antibiotics. The committee were aware of the limitations of the evidence available, including recruitment bias, and considered these limitations when making the recommendations. The committee agreed with your valuable comment that more research is needed to identify the clinical features of cough that would help clinicians target antibiotics appropriately.
Royal College of General Practitioners	Draft Guideline	Page 5 Page 6	Lines 24 to 27 Lines 1 -6	There are concerns that there are lot of over the counter medications here that are given some credence on the basis of "limited evidence suggests that the following have some benefit for the relief of cough symptoms:…." and recommend four types of preparation. These are in the self care category - but of course	Thank you for your comment. The recommendations on over the counter medicines are included within the section on self-care. The wording of this recommendation has been amended to make it clearer that over the counter medicines are for self-care.

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		Page 8 to 12	Line 25 on page 8 to line 3 on page 12	there would be (under duties of a doctor) a duty to prescribe medications that would be beneficial to ease our patients symptoms or cure there problem. Please can NICE clarify they are suggesting self care - and by the nature of a doctors recommendation and the BNF prescribed care involving honey / pelargonium and cough mixtures containing two defined preparations. If these are prescribed it is likely to significantly add to the NHS drug costs	
Royal College of General Practitioners				Consideration of cough caused by ACE inhibitors in prolonged cough Whilst stopping ACE inhibitors should not be initially considered, prolonged coughs in patients on ACE inhibitors may be benefit for withdrawal of the medication	Thank you for your comment. The consideration of non-infective causes of cough, including due to ACE inhibitor use is out of scope for this guideline.
Royal College of General Practitioners		18		Consideration of combination cough suppressant medication A review in BMJ open also considered the use of combination cough suppressant medication https://bmjopenrespres.bmj.com/content/3/1/e000137. The review was funded by Proctor and Gamble This included a study by Mizoguchi *et al* who studied 432 participants in a placebo-controlled study of a syrup containing 15 mg dextromethorphan hydrobromide, 7.5 mg doxylamine succinate, 600 mg paracetamol and 8 mg ephedrine sulfate. The primary end point	Thank you for your comment. The study highlighted by Mizoguchi et al. (2007) was included in the systematic review (Smith et al. 2014), which was included in the evidence review. However, the results from Mizoguchi et al. 2007 were not summarised as not all components of this specific combination cough medicine are available in the UK (doxylamine succinate).

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				(composite of nasal congestion/runny nose/cough/pain relief scores 3 hours postdosing) showed a highly significant beneficial effect in the group given active treatment (p=0.0002). Each individual symptom score also showed statistically significant improvement 3 hours postdosing (p≤0.017). The next morning active treatment continued to show clinically and statistically significant benefits (p≤0.003). Evidence of benefit with the test syrup was also seen in the higher score for overall night-time relief (p<0.0001) and greater satisfaction on sleep (p=0.002). Adverse events were reported at half the frequency in the active treatment group compared with the placebo and there were no reported events >1% in the population. Mizoguchi H, Wilson A, Jerdack GR, et al . Efficacy of a single evening dose of syrup containing paracetamol, dextromethorphan hydrobromide, doxylamine succinate and ephedrine sulfate in subjects with multiple common cold symptoms. Int J Clin Pharmacol Ther 2007;45:230– 6. doi:10.5414/CPP45230	
Royal College of General Practitioners		18		Identification of the effective over the counter cough suppressant products It would be useful to identify which of the current over the counter products may be effective so patents, carers, pharmacists, nurses and GP know which to use. As	Thank you for your comment. Over the counter cough suppressant products (antitussives) were named in the NICE search strategy. Using the evidence identified and their experience, the committee made a recommendation that some people may wish to try cough medicines containing

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				well as a list, these products could have a NICE logo on the box similar to WHICH. Can ineffective over the counter medication be withdrawn?	antitussives, apart from codeine, which did not show evidence of benefit. It is not within NICE's remit to endorse products or suggest over the counter medicines are withdrawn.
Self Care Forum	Guideline	General	General	The Self Care Forum welcomes the draft NICE Guideline on acute cough: antimicrobial prescribing. We further welcome recommendations on when to provide self care advice and agree, in most cases, acute cough is self-limiting and normally lasts around three weeks and does not require antibiotic treatment. The Self Care Forum agrees with the recommendation that people with acute cough and who are not at risk of complications, should be supported to self care and use over-the-counter cough treatments to help with symptom relief.	Thank you for your comments.
Self Care Forum	Guideline	2/3	27 - 5	The Self Care Forum is keen for the NHS to provide information about the normal duration of symptoms and red flags as part of its self care advice to patients and the public and so welcomes this guidance. This information is crucial particularly since many people underestimate the duration of symptoms and seek medical attention too soon as a result. IMS commissioned research from 2009 highlights this and led to the Self Care Forum producing a series of fact sheets with this crucial information pertaining to 14 minor conditions. We suggest the factsheet on cough, which provides advice on normal duration	Thank you for your comment. We have passed this information to our resource endorsement team. More information on endorsement can be found here: NICE Endorsement Programme.

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				and treatment for acute cough and red flags is included as a resource by NICE for healthcare professionals to use in giving self care advice to people, replacing the FP10.	
Self Care Forum	Guideline	5	9-12	Based on the "Home care is best" study in Kingston led by the Self Care Forum's co-chair Dr Pete Smith at his practice and using the NICE guidance for upper respiratory tract infection, delayed antibiotic prescribing as an approach worked very well. Churchill Medical Centre found that delayed prescribing can be a useful tool for GPs particularly if confronted with a sceptical patient who is not happy to leave the surgery without a prescription. In its experience around 70% of these prescriptions are never dispensed.	Thank you for your comment. The committee recognised the usefulness of back-up antibiotic prescriptions in managing self-limiting illness. However, from the evidence, back-up antibiotics were not significantly different to immediate antibiotics or no antibiotics for how long a cough lasts. Therefore, based on evidence, experience and the principles of antimicrobial stewardship, the committee recommended a no antibiotic prescribing strategy (routinely). For most people with an acute cough they felt a back-up antibiotic prescribing strategy sent the wrong message that antibiotics may be needed at some point. This is described in the rationale section of the guideline on back-up antibiotics. The committee agreed, based on experience, that back-up antibiotics could be a useful strategy in such patients on an individualised basis, but on the whole, a recommendation for no antibiotic prescribing was preferred.
Self Care Forum	Guideline	5-6	24-6	The Self Care Forum welcomes the acknowledgement that honey and cough medicines containing pelargonium, guaifenesin or dextromethorphan are effective at treating the symptoms of acute cough and agrees it should be part of self care advice and recommended as a first-line treatment.	Thank you for your comment. The recommendation on self-care using over the counter medicines refers to benefit for the relief of cough symptoms. Therefore, it is believed it is clear that these medicines target the symptoms of an acute cough.

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				It is important to advise people that cough medicines will not 'cure' a cough. If used in accordance with the instructions on the packaging and in the patient information leaflet, then over-the-counter cough medicines are an appropriately safe and effective way to help relieve the disruptive symptoms of a cough so people can get on with their day.	
Self Care Forum	Guideline	6	11-2	The Self Care Forum understands that there is evidence for the effectiveness of pholcodine as a treatment for acute cough. Pholcodine has been used to treat cough since the 1950s and has a long history of well-established use for this indication. In 2012, a review by the European Medicines Agency (EMA) found that "*the existing data is consistent and supportive of the efficacy of pholcodine in the treatment of acute non-productive cough*". This report cites five studies in adults where pholcodine was seen to have a positive effect in acute non-productive cough.	Thank you for your comment. For non-antimicrobial and non-pharmacological interventions, preparations were grouped into classes based on the Cochrane review of over-the-counter preparations (Smith et al. 2014) and other included systematic reviews. The review protocol has been updated to include details on this. These classes were then used by the committee to make decisions on whether to progress down the hierarchy of evidence (from systematic reviews, to RCTs, or further) if there was insufficient evidence; and to limit interventions only to those commonly in use in the UK. For over-the-counter (OTC) preparations, classes were OTC expectorants, OTC antitussives, OTC antihistamines and decongestants, and OTC mucolytics. Pholcodine was considered as part of the class, OTC antitussives. The committee agreed that for these interventions (including OTC antitussives as a class) the systematic review by Smith et al. 2014 provided sufficient evidence, and progressing to RCT evidence was not required. Therefore further evidence on pholcodine (including that provided in the

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					EMA review) as one particular medicine within this class was not included. The included systematic review (Smith et al. 2014) did not include evidence specifically on pholcodine because no placebo-controlled trials were identified which met their inclusion criteria. However, the committee recognised that randomised control trial evidence on pholcodine is available, and the recommendations have been amended to remove reference to specific, named antitussives (apart from codeine), and rather name the class of OTC antitussives (also called cough suppressants).
Self Care Forum	Guideline	36	1-6	The Self Care Forum's aim is to further the reach of self care and embed it in everyone's everyday life so that it becomes an everyday habit and culture. Providing people presenting with symptoms of self-liming conditions with information that they need to become empowered to practice self care is imperative for the individual and to help reduce unnecessary pressure on overstretched NHS services. PAGB research shows that an estimated £810 million a year is spent on unnecessary GP appointments for self-treatable conditions for which self care would have been appropriate and any advice needed could have been provided by a pharmacist. The Self Care Forum is grateful for tools aimed at healthcare professionals, such as this NICE	Thank you for your comments. The guideline includes a section on self-care. The committee agreed that the inclusion of this section is aligned with the views of the Self Care Forum.

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				guidance, to enable them to support people to look after their self-treatable conditions and understand how and when to self care in future. Savings can be made in reducing GP appointments for self-treatable conditions not only because of fewer consultations but also through prescription costs for unnecessary or inappropriate prescribing. The Self Care Forum would like to see more effort in supporting people to understand how to look after their own health better for individuals and to ensure NHS resources are used in the most efficient and effective manner.	
Self Care Forum	General	General	General	The Self Care Forum would like to see more quality studies being published on effective self care and believes this will encourage more take up from both health professionals and individuals. The Self Care Forum also suggests details of Self Care Week (12 – 18 Nov) are included in NICE communications in relation to the guidance. The Self Care Forum organises the awareness week which is aimed at people-facing organisations, such as surgeries, to use as a tool to promote self care messages to their audiences. Self Care Week can be used as a vehicle by health professionals to proactively communicate how people can look after their acute cough and to underline the	Thank you for your comment. Unfortunately, this guideline will publish after self-care week and will not be timely for communications on this.

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				message about antibiotics not being necessary for acute cough. Further details are available on the website.	
British Infection Association	Guideline			In general we support this document	Thank you for your comment.
British Infection Association	General			Whooping cough is mentioned only in children, when it is clear that many cases are being seen in adults. Whether it is worthy of mention is another matter, as we would not advocate diagnostic tests or treatment - by the time it's spotted, it's too late to help the individual or to halt transmission.	Thank you for your comment. We have amended the definition of 'acute cough' in terms used in the guideline to remove the specificity of the population who may experience whooping cough.
British Infection Association	Guideline	4	26	Please add corticosteroids or other immunosuppressants (I remember a disaster in a young woman on methotrexate)	Thank you for your comment. The people who are at higher risk of complications is taken from the NICE guideline on respiratory tract infections (self-limiting): prescribing antibiotics, which does not specify use of other immunosuppressants as a risk factor. Therefore, this recommendation will not be amended.
Proprietary Association of Great Britain	Guideline	General	General	PAGB broadly welcomes the draft NICE Guideline on acute cough. We agree that in the majority of cases acute cough is a self-limiting condition which will last around three weeks and does not require treatment with antibiotics. PAGB fully supports the recommendation that people with acute cough (who are not at high risk of complications) should be advised to self care and use over-the-counter cough treatments to manage their symptoms.	Thank you for your comment.
Proprietary Association of Great Britain	Guideline	2-3	27-5	PAGB fully supports the need to give people with an acute cough self care advice in the first instance.	Thank you for your comment. We have passed this information to our resource endorsement team. More information on

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				Many people are not aware of the normal duration for common minor ailments and underestimate how quickly they will feel better. PAGB research has found that the majority of people (68%) think an acute cough will last between three and six days[1] when it is more likely to last for three to four weeks. The Self Care Forum, a charity supported by PAGB, offers a range of factsheets on self-treatable conditions. The factsheet on cough provides advice on normal duration and treatment for acute cough and red flags which indicate medical advice should be sought. It is available online and could be recommended by NICE as a resource for healthcare professionals to use in giving general self care advice to people[2]. The key to effective management of a cough is to identify the most troublesome symptom and to choose an appropriate product to treat it. The pharmacy should be the first port of call for people who are looking for advice on how to manage their cough symptoms. Pharmacists are expert healthcare professionals who can give advice on the most suitable medicine to take if people are unsure, or signpost people if they need further guidance.	endorsement can be found here: NICE Endorsement Programme. The committee were not able to make a recommendation on the most appropriate health professional to manage people with acute cough, however over the counter medicines available in pharmacies have been recommended as self-care.

[1] PAGB data on file. Survey conducted among 2,000 UK adults in September 2015 by Redshift Research.
[2] Self Care Forum http://www.selfcareforum.org/wp-content/uploads/2013/04/7-Cough.pdf, accessed September 2018.

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Proprietary Association of Great Britain	Guideline	5-6	24-6	PAGB welcomes the acknowledgement in the draft NICE Guidance that cough medicines containing pelargonium, guaifenesin or dextromethorphan are effective at treating the symptoms of acute cough and should be recommended as a first-line treatment. It is important to advise people that cough medicines will not 'cure' a cough. If used in accordance with the instructions on the packaging and in the patient information leaflet, then over-the-counter cough medicines are an appropriately safe and effective way to help relieve the disruptive symptoms of a cough so people can get on with their day.	Thank you for your comment. The recommendation on self-care using over the counter medicines refers to benefit for the relief of cough symptoms. Therefore, it is believed it is clear that these medicines target the symptoms of an acute cough.
Proprietary Association of Great Britain	Guideline	6	11-2	PAGB disagrees that there is a lack of evidence for the effectiveness of pholcodine as a treatment for acute cough. Pholcodine has been used to treat cough since the 1950s and has a long history of well-established use for this indication. In 2012, a review by the European Medicines Agency (EMA) found that "*the existing data is consistent and supportive of the efficacy of pholcodine in the treatment of acute non-productive cough*". This report cites five studies in adults where pholcodine was seen to	Thank you for your comment. For non-antimicrobial and non-pharmacological interventions, preparations were grouped into classes based on the Cochrane review of over-the-counter preparations (Smith et al. 2014) and other included systematic reviews. The review protocol has been updated to include details on this. These classes were then used by the committee to make decisions on whether to progress down the hierarchy of evidence (from systematic reviews, to RCTs, or further) if there was insufficient evidence; and to limit interventions only to those commonly in use in the UK. For over-the-counter (OTC) preparations, classes were OTC expectorants, OTC antitussives, OTC antihistamines and decongestants, and OTC mucolytics.

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				have a positive effect in acute non-productive cough[3]. PAGB would urge NICE to reconsider the evidence for pholcodine as an effective treatment for acute cough in the final guidance.	Pholcodine was considered as part of the class, OTC antitussives. The committee agreed that for these interventions (including OTC antitussives as a class) the systematic review by Smith et al. 2014 provided sufficient evidence, and progressing to RCT evidence was not required. Therefore further evidence on pholcodine (including that provided in the EMA review) as one particular medicine within this class was not included. The included systematic review (Smith et al. 2014) did not include evidence specifically on pholcodine because no placebo-controlled trials were identified which met their inclusion criteria. However, the committee recognised that randomised control trial evidence on pholcodine is available, and the recommendations have been amended to remove reference to specific, named antitussives (apart from codeine), and rather name the class of OTC antitussives (also called cough suppressants).
Proprietary Association of Great Britain	Guideline	36	1-6	PAGB believes it is important to empower people to self care for self-treatable conditions, like acute cough, to help to reduce unnecessary pressure on overstretched NHS services, ensuring people are seen by the right healthcare professional at the right time. An estimated £810 million a year is spent on unnecessary GP appointments for self-treatable conditions for which self	Thank you for your comment. The guideline includes a section on self-care. The committee agreed that the inclusion of this section is aligned with the views of the Proprietary Association of Great Britain.

[3] European Medicines Agency (2012) http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Pholcodine_31/WC500124716.pdf, accessed September 2018.

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				care would have been appropriate and any advice needed could have been provided by a pharmacist[4]. A reduction in GP appointments for self-treatable conditions will also release savings in prescription costs for unnecessary or inappropriate prescribing. PAGB is calling for a national strategy for self care to ensure appropriate policies are put in place to support people to self care when it is appropriate to ensure NHS resources are used in the most efficient and effective manner.	
British Thoracic Society	General			Overall the guideline provides sensible advice and fairly represents existing evidence in this area. The British Thoracic Society (BTS) had no prior knowledge of the preparation of this guideline and we note that the guideline development group did not include respiratory expertise.	Thank you for your comment. A respiratory specialist (Dr Tim Felton, Consultant in Intensive Care and Respiratory Medicine at Manchester University NHS Foundation Trust) has been recruited to the committee for this guideline to provide expertise and experience. Their views have been sought on a post-consultation version of the guideline and they will continue to contribute as appropriate in the development and finalisation of this guideline.
British Thoracic Society	General			We are concerned that there is little mention of acute cough representing an exacerbation of pulmonary diseases such as asthma, where antibiotics may well still be inappropriate but the exacerbation does need treating. Is there a risk that those reading this guidance may misinterpret the sections on bronchodilators and corticosteroids which	Thank you for your comment. This was discussed by the committee and the recommendation has been amended, to be clearer that these interventions are not recommended for the sole purpose of treating acute cough and in the absence of asthma. Readers are directed to relevant NICE guidelines on exacerbations of other pulmonary conditions, including chronic

[4] PAGB (2018) A long-term vision for self care: interim White Paper https://www.pagb.co.uk/content/uploads/2018/07/A-long-term-vision-for-self-care-interim-white-paper.pdf, accessed September 2018.

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				aren't effective for acute cough in otherwise healthy individuals but may be needed in those with underlying airways disease and an exacerbation?	obstructive pulmonary disease and bronchiectasis in the overview section, and these conditions are not covered in this guideline.
British Thoracic Society	Question 1			1. *Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why.* The guidelines do not contain any new or surprising recommendations; overall they reinforce current thinking on the management of acute cough. It has long been recognised that the majority of acute cough is viral and therefore the role for antibiotics is limited. Equally the evidence that any antitussive treatments are effective is weak/lacking. However cough is a very unpleasant symptom which significantly impacts upon patients' quality of life, so healthcare professionals inevitably feel a pressure to prescribe something and this has always been the challenge, especially for primary care physicians. Phasing out antibiotic prescription for most-will have significant impact in general practice and requires significant public education (honey, not antibiotics.)	Thank you for your comment.
British Thoracic Society	Question 2			2. *Would implementation of any of the draft recommendations have significant cost implications?*	Thank you for your comment.

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				No, these should save money as hopefully they will reduce further inappropriate prescribing of antibiotics.	
British Thoracic Society	Question 3			*3. What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.)* Initiatives to improve public awareness of the lack of effect/ risks associated with the use of antibiotics for acute cough. The recent increased efforts in the development of new cough treatments may in future help to alleviate the challenge faced by physicians pressured to provide a treatment for acute cough. Currently new treatments are in development for chronic cough but should they prove to also be effective in acute cough, then alternatives to antibiotics and poorly effective OTC anti-tussives may become an option.	Thank you for your comment. This guideline will be reviewed to ensure it remains up to date, in line with the methods in the Interim process guideline (section 14) and Developing NICE guidelines the manual (section 13). Any new treatments for acute cough will be considered during the review of the guideline.
British Thoracic Society	Question 4			*4. For the **guideline**:* o *Are there any recommendations that will be a significant change to practice or will be difficult to implement? If so, please give reasons why.* Unlikely to be a significant change to practice, main difficulty in implementation	Thank you for your comment.

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				is the lack of availability of effective treatment options. ○ What are the key issues or learning points for professional groups? The key issues are the lack of effectiveness of antibiotics/ antitussives in acute cough and the risks associated with inappropriate use. However this knowledge is well-established and so the guideline mainly serves to firm up existing knowledge.	
British Thoracic Society	Guideline	Page 2	1.1	Worth mentioning that the cough reflex is more sensitive during an acute URT infection and then normalises on recovery[1]. This is conceptually important when dealing with acute cough and can be helpful information for patients trying to understand what is going on.	Thank you for your comment. The committee considered the mechanism of acute cough during an upper respiratory tract infection, however agreed not to include this detail within the recommendations. The reference provided (Dicpinigatis, Tibb et al. 2014) will not be included in the evidence review as it is not a study evaluating the effectiveness of an intervention.
British Thoracic Society	Guideline	Page 3	1.1.6	Add montelukast to the list of drugs not worth prescribing[2].	Thank you for your comment. For non-antimicrobial and non-pharmacological interventions, preparations were grouped into classes based on included systematic reviews. The review protocol has been updated to include details on this. These classes were then used by the committee to make decisions on whether to progress down the hierarchy of evidence (from systematic reviews, to RCTs, or further) if there was insufficient evidence; and to limit interventions only to those commonly in use in the UK.

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					For montelukast, this was included within the class leukotriene receptor antagonists. No systematic reviews on leukotriene receptor antagonists were included as they did not meet the review protocol. And the committee agreed that there was no requirement to look further than this for evidence on leukotriene receptor antagonists because this class of medicine is not commonly in use for acute cough. Montelukast is licensed for prophylaxis of asthma and symptomatic relief of seasonal allergic rhinitis in patients with asthma. The reference provided (Wang et al. 2014) was therefore not included.
British Thoracic Society	Guideiine	Page 5	1.2	It would be worth mentioning at this point the general principle underlying cough remedies, i.e. the complex mechanisms in addition to the pharmacological effect of the active drug. The placebo effect is often marked (and treatment with something is often better than no treatment at all) and other poorly understood actions such as a 'physiological effect' (and voluntary control, natural resolution and regression to the mean) may be important[3]. Cough medicines often have sapid, glycerine like consistency that may be important and sweet taste has been shown to supress the cough reflex[4] (possibly why honey has an effect). This point is important when thinking about what is being prescribing and what these medicines are actually doing, particularly given the very weak and conflicting	Thank you for your comment. The committee considered this and has added further detail to the rationale around the placebo effect and the possibility that the sweetness and consistency of cough medicines could be important. The committee were aware of the possible mechanism of action of simple linctus, and appreciated that there is limited evidence on all over the counter medicines. Therefore, the reference to simple linctus was removed from the recommendations. The references provided (Eccles et al. 2010 and Wise et al. 2014) have not been included in the evidence review as they are narrative reviews.

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				evidence for the use of these medicines. On this basis is it wise to dismiss the use of simple linctus? We appreciate the evidence base here is lacking but that applies to all the medicines listed here.	
British Thoracic Society	Guideline	Page 5	1.2.1	This is a difficult area as the evidence base is sparse and therefore the process of guideline production tricky as the committee noted. The recommendation for honey is reasonable. The wording here possibly overstates the potential effectiveness of other medications (particularly pelargonium and to a slightly lesser extent guaifenesin dextromethorphan). To our knowledge there are no trials of acceptable standard looking at these medications and results from what studies there have been have been contradictory[5]. The best that can be said is that they *may* have some effect. It is important not to dismiss all these medications outright given the lack of definitive evidence, although we note the ACCP takes a contrary view on the area of OTC cough remedies, advising against their use altogether [6]. The effects of these medicines should be seen in the context of a complex action-placebo, physiological effect, natural resolution/regression to the mean, voluntary control etc. Should the potential adverse effects of dextromethorphan be mentioned? There is absolutely no mention of menthol, a common component in cough remedies. We appreciate there is very little evidence here[5] but there should be	Thank you for your comment. The recommendations on over the counter medicines for acute cough have been amended to reflect the strength of evidence. The committee recognised that dextromethorphan may increase adverse effects, as described in the rationale section of the guideline. The committee also recognised limitations with the evidence on dextromethorphan (which is for a single high dose) and agreed that it should not be specifically named as an antitussive which may have benefit, therefore this recommendation has been amended to reflect this. For non-antimicrobial and non-pharmacological interventions, preparations were grouped into classes based on the Cochrane review of over-the-counter preparations (Smith et al. 2014) and other included systematic reviews. The review protocol has been updated to include details on this. These classes were then used by the committee to make decisions on whether to progress down the hierarchy of evidence (from systematic reviews, to RCTs, or further) if there was insufficient evidence; and to limit interventions only to those commonly in use in the UK.

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				some discussion even just to state that there is no evidence? References for above: 1. Dicpinigaitis PV, Tibb AS, Ramsey DL, Carr AN, Poore CL. Stability of cough reflex sensitivity during viral upper respiratory tract infection (common cold). Pulm Pharmacol Ther. 2014 Aug;28(2):154-7. doi: 10.1016/j.pupt.2014.05.004. Epub 2014 May 28. PubMed PMID: 24878421. 2. Wang K, Birring SS, Taylor K, Fry NK, Hay AD, Moore M, Jin J, Perera R, Farmer A, Little P, Harrison TG, Mant D, Harnden A. Montelukast for postinfectious cough in adults: a double-blind randomised placebo-controlled trial. Lancet Respir Med. 2014 Jan;2(1):35-43. doi: 10.1016/S2213-2600(13)70245-5. Epub 2013 Dec 2. PubMed PMID: 24461900. 3. Eccles R. Importance of placebo effect in cough clinical trials. Lung. 2010 Jan;188 Suppl 1:S53-61. doi: 10.1007/s00408-009-9173-3. Epub 2009 Sep 16. PubMed PMID: 19760296. 4. Wise PM, Breslin PA, Dalton P. Effect of taste sensation on cough reflex sensitivity. Lung. 2014 Feb;192(1):9-13. doi: 10.1007/s00408-013-9515-z. Epub2013 Oct 31. Review. PubMed PMID: 24173385.	For over-the-counter (OTC) preparations, classes were OTC expectorants, OTC antitussives, OTC antihistamines and decongestants, and OTC mucolytics. The committee agreed that for these interventions, the systematic review by Smith et al. 2014 provided sufficient evidence, and progressing to RCT evidence was not required. The committee also agreed that the systematic review included all commonly used OTC preparations and there was no requirement to look further than this for evidence on OTC preparations not included in this review (such as menthol). The references provided here have not been included in the evidence review as they do not meet the review protocol: Dicpinigaitis et al. 2014 is a narrative review and Malesker et al. 2017 is other guidance (other references included here have been addressed in relevant comment responses).

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				5. Dicpinigaitis PV, Morice AH, Birring SS, McGarvey L, Smith JA, Canning BJ, Page CP. Antitussive drugs--past, present, and future. Pharmacol Rev. 2014 Mar 26;66(2):468-512. doi: 10.1124/pr.111.005116. Print 2014. Review. PubMed PMID: 24671376. 6. Malesker MA, Callahan-Lyon P, Ireland B, Irwin RS; CHEST Expert Cough Panel. Pharmacologic and Nonpharmacologic Treatment for Acute Cough Associated With the Common Cold: CHEST Expert Panel Report. Chest. 2017 Nov;152(5):1021-1037. doi: 10.1016/j.chest.2017.08.009. Epub 2017 Aug 22. Review. PubMed PMID: 28837801; PubMed Central PMCID: PMC6026258.	
Department of Health and Social Care				Advised that they have no comments to submit on this occasion	Thank you for your comment.
GlaxoSmithKline		General	General	GSK would like to thank NICE for its work on the development of the guideline on Cough (acute): antimicrobial prescribing and for the opportunity to comment on the draft clinical guideline.	Thank you for your comment.
GlaxoSmithKline	Guideline	6	1	GSK supports the NICE position on the expectorant guaifenesin. Guaifenesin is an expectorant indicated to help loosen phlegm (mucus) and thin bronchial secretions to promote expectoration and make cough more productive.	Thank you for your comment.
GlaxoSmithKline	Guideline	6	3	GSK is aligned with the NICE position on the antitussive dextromethorphan. Dextromethorphan is indicated as an	Thank you for your comment. The committee recognised limitations with the evidence on dextromethorphan (which is for a single high

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				antitussive, for the relief of an unproductive cough.	dose) as well as an association with adverse events and agreed that it should not be specifically named as an antitussive which may have benefit. The recommendations have been amended to remove the specific reference to dextromethorphan, and now say, cough medicines containing antitussives (apart from codeine) may wish to be tried. This change also reflects consultation comments regarding pholcodine (see other responses).
GlaxoSmithKline	Guideline	6	11	The draft guideline currently states: "no evidence for cough medicine containing pholcodine or simple linctus was found." GSK notes that the use of pholcodine for the treatment of acute cough was assessed by the European Medical Agency (EMA), (Procedure number: EMEA/H/A-31/1292, dated 17th of February 2012) "Assessment report for Pholcodine containing medicinal products", (http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Pholcodine_31/WC500124716.pdf) EMA reviewed the clinical efficacy and safety of pholcodine for the treatment of unproductive cough and in the Overall Conclusion session stated that: "The Committee also shows that data from clinical trials and extensive post marketing use has demonstrated the efficacy of pholcodine in the treatment of non-productive cough. The Committee concluded that the benefit-risk balance of pholcodine-containing products in the treatment of	Thank you for your comment. This wording has been removed. For non-antimicrobial and non-pharmacological interventions, preparations were grouped into classes based on the Cochrane review of over-the-counter preparations (Smith et al. 2014) and other included systematic reviews. The review protocol has been updated to include details on this. These classes were then used by the committee to make decisions on whether to progress down the hierarchy of evidence (from systematic reviews, to RCTs, or further) if there was insufficient evidence; and to limit interventions only to those commonly in use in the UK. For over-the-counter (OTC) preparations, classes were OTC expectorants, OTC antitussives, OTC antihistamines and decongestants, and OTC mucolytics. Pholcodine was considered as part of the class, OTC antitussives. The committee agreed that for these interventions (including OTC antitussives as a class) the systematic

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				non-productive cough is positive under normal conditions of use." The following six publications were included in the clinical data section of the EMA's Assessment: 1) Comparative efficacy and tolerability of pholcodine and dextromethorphan in the management of patients with acute, non-productive cough: a randomized, double-blind, multicenter study. Equinozzi R, Robuschi M; Italian Investigational Study Group on Pholcodine in Acute Cough. Treat Respir Med. 2006;5(6):509-13 2) Randomized single-blind trial in general practice comparing the efficacy and palatability of two cough linctus preparations, 'Pholcolix' and 'Actifed' Compound, in children with acute cough. Jaffé G, Grimshaw JJ. Curr Med Res Opin. 1983;8(8):594-9. 3) Pholcodine plus pseudoephedrine in the treatment of cough. A controlled trial. Rose JR. Practitioner. 1967 May;198(187):704-7. 4) A comparative clinical test of pholcodine with codeine as control. Kelly DF. Northwest Med. 1963 Nov; 62:871-4. 5) Clinical investigation of antitussive properties of pholcodine. Mulinos MG, Nair KG, Epstein IG. N Y State J Med. 1962 Jul 15;62:2373-7. 6) Preliminary evaluation of pholcodine, a new antitussive agent. Heffron CE. J New Drugs. 1961 Sep-Oct; 1:217-22.	review by Smith et al. 2014 provided sufficient evidence, and progressing to RCT evidence was not required. Therefore further evidence on pholcodine (including that provided in the EMA review) as one particular medicine within this class was not included. The included systematic review (Smith et al. 2014) did not include evidence specifically on pholcodine because no placebo-controlled trials were identified which met their inclusion criteria. However, the committee recognised that randomised control trial evidence on pholcodine is available, and the recommendations have been amended to remove reference to specific, named antitussives (apart from codeine), and rather name the class of OTC antitussives (also called cough suppressants).

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				Based on the above, GSK would propose this evidence is considered in NICE's "Evidence Summary" under section 3.2.3 Antitussives, as well as a recommendation to use pholcodine in acute cough as an additional self-care medicine option under section 1.2.1 (page 6) and OTC antitussives section (pages 14 and 19) of the Guideline.	
GlaxoSmithKline	Guideline	6	8	The draft guideline currently states: "limited evidence suggests that antihistamines, decongestants and cough medicines containing the antitussive codeine do not help cough symptoms." GSK agrees that there is limited evidence on the efficacy of decongestant and codeine containing products to help cough symptoms. However, GSK requests NICE to consider antihistamine to be divided into: first-generation (clemastine, diphenhydramine, chlorphenamine, promethazine) and second-generation (loratadine, cetirizine). GSK agrees that second-generation antihistamines have not demonstrated a clinical benefit in in reducing the cough symptoms associate with cold and flu. GSK notes that for first-generation antihistamines the clinical evidence presented in the NICE draft guideline is solely based on the Smith et al. 2014 Cochrane Systematic Review "Over-the-counter (OTC) medications for acute cough in children and adults in community settings."	Thank you for your comment. For non-antimicrobial and non-pharmacological interventions, preparations were grouped into classes based on the Cochrane review of over-the-counter preparations (Smith et al. 2014) and other included systematic reviews. The review protocol has been updated to include details on this. These classes were then used by the committee to make decisions on whether to progress down the hierarchy of evidence (from systematic reviews, to RCTs, or further) if there was insufficient evidence; and to limit interventions only to those commonly in use in the UK. For over-the-counter (OTC) preparations, classes were OTC expectorants, OTC antitussives, OTC antihistamines, OTC decongestants, and OTC mucolytics. The committee agreed that OTC antihistamines could be presented as a class, as in the systematic review by Smith et al. 2014, and not separated into first- and second-generation. They also agreed that Smith et al. 2014 provided sufficient evidence on classes of

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				However, the authors of this systematic review were unable to carry out meta-analyses because the studies were too heterogeneous and provided insufficient data. GSK would like to draw NICE attention on clinical data, even if limited, in support of the use of first-generation antihistamines containing medicinal products for the treatment of cough associated with cold and flu and in particular on diphenhydramine. Morice and Kardos in 2016 have published a review titled: "Comprehensive evidence-based review on European antitussives" including diphenhydramine providing the following evidence: "Diphenhydramine is a first-generation H1 antihistamine approved as an OTC antitussive in the USA and the UK. First-generation antitussives in combination with oral decongestants are recommended by the American College of Chest Physicians Evidence Based Guidelines for the treatment of cough in common cold and in the so-called upper airway cough syndrome. GSK acknowledges that this recommendation is based on expert opinion. In cough challenge studies in healthy participants and patients with acute viral respiratory infection (diphenhydramine combination syrup with decongestant) in adults, efficacy could have been established. However, no symptom or objective cough monitoring-based studies are available	OTC medicines, and progressing to RCT evidence was not required. Therefore further evidence on antihistamines was not included. The references provided were therefore not included, and in addition: Morice and Kardos 2016 – would have been excluded on study type (narrative review) Irwin et al. 2006 – executive summary of other guidance Packman et al. 1991 – would have been excluded on population (participants do not have acute cough) Dicpinigaitis et al. 2015 – would have been excluded on population (unclear if participants have acute cough) Howard et al. 1979 – would have been excluded based on date (pre-2005; unable to identify from detail provided) Crutcher et al. 1981 – would have been excluded based on date (pre-2005; unable to identify from detail provided)

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				for acute cough. There is a clear-cut discrepancy between evidence of efficacy and broad clinical use of diphenhydramine/decongestant combinations for acute cough, despite a sedative effect (dizziness), especially in the USA." The review from Morice and Kardos included the following publications, none of which were included in the Cochrane Systematic Review: 1) Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. Irwin RS, Baumann MH, Bolser DC, et al. (ACCP) ACoCP. Chest 2006;129:1S–23S. 2) Chronic cough. Lancet 1981;2:907–8. 3) Antitussive effects of diphenhydramine on the citric acid aerosol-induced cough response in humans. . Packman EW, Ciccone PE, Wilson J, et al. Int J Clin Pharmacol Ther Toxicol.1991;29:218–22. 4) Inhibition of cough reflex sensitivity by diphenhydramine during acute viral respiratory tract infection. Dicpinigaitis PV, Dhar S, Johnson A, et al. Int J Clin Pharm 2015;37:471–4. Two studies from Howard et al. (1979) and Crutcher (1981), showed that another first-generation antihistamine, chlorpheramine, used in patients suffering from the common cold, was able to significantly reduce the total	

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				subjective score, including cough, up to seven days. Additionally, there is some clinical evidence that first generation antihistamines have a limited short-term beneficial effect on the severity of overall cold symptoms (days one and two of treatment). Based on the above, GSK would propose this evidence is considered in NICE's "Evidence Summary" under section 3.2.4 Antihistamine and decongestants, as well as a recommendation to use diphenhydramine in acute cough as an additional self-care medicine option under section 1.2.2 (page 6) and OTC Antihistamine and decongestants section (pages 15 and 19) of the Guideline.	
Royal College of Nursing				Advised that they have no comments to submit on this occasion	Thank you for your comment.
Royal College of Paediatrics and Child Health				General comments • This represents an important and worthwhile topic to provide guidance on. • Would it be easier to follow if the guideline had a discrete paediatric section? The guideline covers the paediatric age group but disappointing to see lack of obvious representation from those with specific paediatric expertise on the panel	Thank you for your comments. Based on the evidence identified and their experience, the committee agreed that the recommendations were applicable across all ages, unless an age restriction was included in an individual recommendation (for example for some over the counter medicines). Therefore, a discrete paediatric section would lead to repetition of recommendations. However, an antibiotic choice table specifically for children and young people under 18 years is included in the guideline. The standing committee for this suite of antimicrobial prescribing guidelines were formed in line with the Interim process and methods guide, and Developing NICE

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					guidelines: the manual, and the committee includes a paediatric microbiologist.
Royal College of Paediatrics and Child Health		3	6	In children cough associated with fever >48 hours and shortness of breath is still a good candidate for amoxicillin treatment [expert opinion]	Thank you for your comments. Based on the evidence available, the committee were unable to provide a definitive list of people in whom it may be appropriate to prescribe an antibiotic, including in children. An immediate antibiotic is recommended for people (including children) who are 'systemically very unwell', and either an immediate or back-up antibiotic is recommended for people (including children) who are at a higher risk of complications (which includes young children born prematurely). It is also recommended that for children under 5 with an acute cough and fever, the NICE guideline on fever in under 5s is followed. Amoxicillin is recommended as the first choice antibiotic in children for acute cough, if an antibiotic is appropriate.
Royal College of Paediatrics and Child Health		5	24	Acute cough in the absence of fever and SOB in another wise healthy child should not be routinely treated with anything other than honey (contraindicated in infants). The evidence for this is summarised 2 Cochrane reviews (Oduwole et al 2014 and Smith et al 2014 - see full references below. It is largely covered in the more detailed discussion of the evidence in the document (pages 8-19) although the way they have presented it is a mixture of adult and paediatric information.) Oduwole O, Meremikwu MM, Oyo-Ita A, Udoh EE. Honey for acute cough in	Thank you for your comments. The recommendations have been amended to specify that all self-care options other than honey are indicated in people aged 12 and over. The references provided (Oduwole et al. 2014 and Smith et al. 2014) are both included in the evidence review and were considered by the committee when making the recommendations.

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				children. Cochrane Database of Systematic Reviews 2014, Issue 12. Art. No.: CD007094. DOI: 10.1002/14651858.CD007094.pub4. Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in community settings. Cochrane Database of Systematic Reviews 2014, Issue 11. Art. No.: CD001831. DOI: 10.1002/14651858.CD001831.pub5.	