National Institute for Health and Care Excellence

Pneumonia
Guideline Consultation Table
18/06/14-30/07/14

ID	Type	Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
57	SH	Aspire	1	Appendix O	IV antibiotics		The cost of Zedbac (azithromycin) 500mg powder for solution for infusion has not been included and does not appear to have been considered, despite it being available on the market since September 2013. Current cost for a 500mg vial of Zedbac is £9.50 and the daily dosage is 500mg, once daily.	Thank you for your comment. The costs presented in the guideline were based on the BNF65 and MIMS accessed in April 2013, the time when this evidence was presented to the GDG. The GDG made recommendations based on the available products at that time. Further to your comment, we have now included the new product to the list and the GDG has considered it.
8	SH	The Royal College of Radiologists in collaboration with The British Society of Thoracic Imaging	1	FULL	General	General	In the NICE recommendations for diagnostic tests for both CAP and HAP, chest radiography is not mentioned, despite radiographic studies having been evaluated. The way it stands, the NICE guidelines imply that chest radiography is not a clinically useful or cost effective method of diagnosing pneumonia. Is this because it is part of the diagnostic criteria used? It is such a central diagnostic test in the assessment of patients with suspected pneumonia, that its role needs to be clarified.	Thank you for your comment. The GDG agree that chest X-Ray (CXR) is a central diagnostic test and included this in the definition of pneumonia. Further comment on this subject is made in the introduction on pages 14 and 15 in which CXR is referred to as the "Gold standard" diagnostic test. The developers have added a sentence to the "terms used in this guideline" for both CAP and HAP in the NICE version to highlight that CXR is required to make a definitive diagnosis. The developers have also included chest x-rays in the recommendation to reflect the importance of x-rays as part of the diagnostic criteria for pneumonia.
9	SH	The Royal College of Radiologists in	2	FULL	General	General	The Full recommendations state that CXR is not available to GPs or there is significant delay in chest radiographic reporting for GPs. In many	Thank you for your comment. The introduction to chapter 7 states: "While it is available to and used by GPs, it is not

		collaboration with The British Society of Thoracic Imaging					hospitals, all GP CXRs are shown to a Radiologist before the patient leaves the department, in case of major pathology which needs treating. This is the case in every Radiology Department I have worked in and should be highlighted as good standard of care. Simply to ignore chest radiography as a diagnostic test does not reflect current medical practice.	available in GP surgeries and CXR reporting to the GP may be delayed, limiting its clinical usefulness in primary care." The GDG reiterates this view and that a *clinical* diagnosis of pneumonia by a GP in a low risk patient is a pragmatic strategy in primary care (with referral to a hospital for a CXR not always being necessary). The developers have added a sentence to the "terms used in this guideline" for both CAP and HAP in the NICE version to highlight that CXR is required to make a definitive diagnosis.
10	SH	The Royal College of Radiologists in collaboration with The British Society of Thoracic Imaging	3	FULL	General	General	There was no Radiologist involved in the Guideline Development Group, which was questioned by The Royal College of Radiologists at the outset when the guideline development group was being recruited, and likely results in the above comments.	Thank you for your comment. While the GDG agrees that it would have been ideal for many different clinical specialties, including a radiologist, to be represented on the GDG, for practical reasons representatives must be prioritised based on the topics defined in the scope. As stated in the preceding response, a chest x-ray is an acknowledged central test in the diagnosis of pneumonia in hospitals, and its role therefore not a matter of debate.
34		UK Clinical Pharmacy Association (UKCPA) Respiratory Group & Pharmacy Infection Network (PIN	14	FULL	General	General	The text below is copied from the draft guideline (Page 263) "For patients with high-severity CAP, a recommendation for a beta-lactamase stable beta-lactam plus macrolide was agreed by GDG consensus. The GDG felt the mortality rate associated with high-severity CAP to be sufficiently high to justify using broad-spectrum empirical therapy despite the potential adverse effects associated with antibiotic therapy such as beta-lactamase stable beta-lactams." "The GDG debated how specific the recommendation relating to beta-lactam and	Thank you for your comments. The GDG discussed the wording of the antibiotic therapy recommendations extensively, with numerous factors taken into consideration. To address your specific points: The GDG acknowledge that a proportion of UK hospitals use a narrow-spectrum penicillin (such as benzyl-penicillin) as the beta-lactam component for treating high-severity CAP. However it is noted that the reference you cite is an abstract (not a published paper) and NICE does

							macrolide should be. For patients with high-severity CAP, the GDG noted that some hospitals currently use intravenous second generation cephalosporins or antipseudomonal penicillins (such as piperacillin-tazobactam) as the "beta-lactam" component of dual therapy. The GDG felt that co-amoxiclav was likely to be the most reasonable first-line choice on the basis of antimicrobial spectrum, cost, oral step-down availability and C. difficile rates. However, the GDG acknowledged that there was little robust evidence to suggest that alternative beta-lactamase stable beta-lactams were inferior, and therefore named co-amoxiclav as an example rather than a specific recommendation. For the macrolide component, the GDG felt that naming clarithromycin as an example was justified based on side-effect profile and cost." Comment below is in response to the above section of the guideline. The GDG has not acknowledged that many UK hospitals use a narrow-spectrum penicillin (benzylpenicillin) for severe CAP. A 2013 survey of over 100 acute Trusts revealed that more than 25% of hospitals used benzylpenicillin for severe CAP [http://eccmid.meetingxpert.net/ECCMID_699/poster_113438/program.aspx/anchor113438]. This represents a significant body of UK medical opinion that deserves acknowledgement in the NICE guideline. Presumably, the decision to recommend benzylpenicillin as a 'backbone' agent for severe CAP is related to clinical experience and emerging evidence that co-amoxiclav is a high-risk agent for predisposing patients to Clostridium difficile infection [e.g. Vernaz N 2009 https://www.pubmed.org/pubmed/19372170 ;	not routinely include abstracts in systematic reviews. The recommendation to "consider dual therapy" including a beta-lactamase stable beta-lactam was reached by GDG consensus. The GDG felt that the mortality of high-severity CAP is sufficiently high to support the use of a broad-spectrum (i.e. beta-lactamase stable) beta-lactam, as it makes sense to empirically cover as many potential causative pathogens as possible – treatment failure in high-severity CAP is associated with a very high rate of complications and mortality. This equates to approximately a quarter of the patients (28% in the last BTS audit) treated in hospital (i.e. CURB65 3 or above). The additional gram-negative, staphylococcal and other cover afforded by beta-lactamase stable beta-lactams was considered to outweigh the possible increased risk of adverse effects associated with antibiotic therapy. The GDG agreed that the most important threat associated with antibiotic use is due to incorrect or over-diagnosis of CAP, hence the emphasis on early and accurate diagnosis and antibiotic stewardship emphasised in other areas of the guideline. Other sections of the guideline support the use of microbiological tests to identify the causative pathogen(s) in high-severity CAP. Whilst not specifically recommended (as this is beyond the scope of the guidance), the GDG

							Talpaert M 2011 https://www.pubmed.org/pubmed/21676904 ; Chilton CH 2012 https://www.pubmed.org/pubmed/22279183]. Given this evidence of risk associated with co-amoxiclav, would the GDG consider offering a choice of beta-lactamase stable beta-lactams (i.e. co-amoxiclav or cefuroxime or cefotaxime or ceftriaxone)? There seems to be no evidence to suggest that any of these agents are superior for efficacy or comparably lower risk for selecting Clostridium difficile. The decision by the NICE GDG to recommend a beta-lactamase stable penicillin appears to have been based on GDG consensus rather than any evidence of superiority. In Table 101, the Gaillat 1994 study showed comparable outcomes for a narrow-spectrum penicillin (benzylpenicillin) in combination with ofloxacin when compared with co-amoxiclav with erythromycin. However, patient numbers were very low in this study and the GDG quite rightly points out that reported low mortality suggests the trial patient population may not be comparable with UK patients with severe pneumonia. Would the GDG consider offering a benzylpenicillin plus macrolide/tetracycline/fluoroquinolone regimen for patients with severe CAP and no risk factors for Gram-negative enterobacteriaceae? No consideration of pathogen epidemiology in severe pneumonia is evident. Can the GDG consensus to recommend a beta-lactamase stable penicillin be supported by evidence from pathogen epidemiology studies? If mortality is largely accounted for by S. pneumonia, then how can the GDG reconcile the relatively low dose of amoxicillin in the licensed dose of co-amoxiclav (1g 8-hourly) in comparison to the potential to treat with	acknowledge that narrowing/focussing of antibiotic treatment may be appropriate after a specific organism is identified. The scope did not include management of people at risk for specific pathogens, such as enterobacteriacaea and therefore including such a caveat in a recommendation is beyond the scope of this guidance. The GDG have not given a negative ("do not offer") recommendation to the alternatives you have suggested, and acknowledged during their discussions and the evidence and link to recommendations table that some local policies will specify alternative specific agents. With regards to the question on epidemiology, the developers have considered this. Please refer to appendix N. Specific dose recommendations are usually not included in NICE guidance. Prescribers are expected to refer to relevant SmPCs prior to prescribing. However, the GDG felt that the standard licensed dose of co-amoxiclav used in the UK would be sufficient as empirical therapy in high-severity CAP.

							benzylpenicillin at a dose of 2.4g 6-hourly? Would the GDG consider offering the option of co-amoxiclav 1.2g iv 8-hourly with the addition of amoxicillin 1g iv 8-hourly?	
28		UK Clinical Pharmacy Association (UKCPA) Respiratory Group & Pharmacy Infection Network (PIN	8	FULL	General	General	How has the committee reached the conclusion that amoxicillin is the most common antibiotic prescribed for CAP? PHE guidelines (link) are for amoxicillin/clarithromycin/doxycycline with no clear preference and it is believed that a lot of hospital trusts are using doxycycline first line. The evidence behind this conclusion should be referenced if it is to remain. The following statement has been questioned as the evidence does not point to amoxicillin (or any drug) being superior in clinical efficacy or toxicity to another: "Consider amoxicillin in preference to a macrolide or tetracycline for patients with low-severity community-acquired pneumonia. Consider a macrolide or tetracycline for patients who are allergic to penicillin"	Thank you for your comments. Although the GDG experience is that amoxicillin is the most widely used, we accept that it is difficult to prove this and have amended the sentence to state that amoxicillin is one of the most commonly prescribed antibiotics for low-severity CAP. The GDG agree that there is a paucity of evidence and agreed the recommendation to "consider" amoxicillin in preference to a macrolide or tetracycline by GDG consensus. Several factors were taken into consideration when making this recommendation. Macrolide resistance is not a major problem in the UK at present but has been developing in other countries such as the USA. An indirect comparison of amoxicillin and clarithromycin (as no direct evidence was available) suggested that amoxicillin treatment was associated with a lower rate of adverse event withdrawals than clarithromycin, which correlated with the GDG's experience and consensus. Tetracyclines such as doxycycline were considered. The GDG considered the narrow spectrum of amoxicillin, side-effect profile (for example, photosensitivity with doxycycline), safety in pregnancy (dental effects with doxycycline), absorption (decreased for doxycycline with calcium/dairy intake) and other factors to

								be advantageous, and concluded that recommending amoxicillin as a specific agent was justified for simplicity. The GDG acknowledged that there is a paucity of evidence in this area, and that doxycycline and macrolides were reasonable alternative treatments, hence the recommendation to "consider" rather than specifically "offer" amoxicillin.
32		UK Clinical Pharmacy Association (UKCPA) Respiratory Group & Pharmacy Infection Network (PIN)	12	FULL	General	General	Currently the recommendation of a 5- to 10-day course of antibiotics for hospital acquired pneumonia is not helpful without the small text that this depends on response to treatment, severity (although section 16 tells us that there is no data to define severity of HAP), co-morbidity and complications.	Thank you for your comment. The GDG debated how best to word this recommendation. In the absence of any convincing evidence to recommend a specific duration of treatment, the GDG recommended a range of durations. The factors that need to be taken into account are numerous – to list all the specific patient and illness factors within the recommendation would not be feasible. Taking all these factors into account is an inherent part of clinical judgement, and specific details on how to assess these factors was considered to be inappropriate in the absence of good evidence to support them.
31		UK Clinical Pharmacy Association (UKCPA) Respiratory Group & Pharmacy Infection Network (PIN	11	FULL	General	General	Although briefly discussed in 8.11.1, clinical judgement isn't given sufficient prominence and could easily be overlooked in practice. There is also a lack of consideration of other supportive therapies (e.g. oxygen, fluids, VTE risk)	It is a principle underlying all clinical guidelines that these do not replace, and should be used in conjunction with, clinical judgement. Other supportive therapies were excluded in the scope (see section 4.3.2d).
33		UK Clinical Pharmacy Association (UKCPA)	13	FULL	General	General	More detail should be included in the shortened guideline regarding course length. For moderate and severe CAP when should a 7-day course be prescribed, and when should a 10 day course be	Thank you for your comment. The GDG debated how best to word this recommendation. In the absence of any convincing evidence to recommend a

		Respiratory Group & Pharmacy Infection Network (PIN					prescribed? For HAP when should a 5-day course be prescribed, and when should a 10 day course be prescribed?	specific duration of treatment, the GDG recommended a range of durations. The factors that need to be taken into account are numerous – to list all the specific patient and illness factors within the recommendation would not be feasible. Taking all these factors into account is an inherent part of clinical judgement, and specific details on how to assess these factors was considered to be inappropriate in the absence of good evidence to support them.
24	SH	UK Clinical Pharmacy Association (UKCPA) Respiratory Group & Pharmacy Infection Network (PIN)	4	FULL	General	General	With regards to recommendations in primary care to use CRP testing to determine whether or not to offer antibiotics, or to offer a delayed prescription, can CRP testing be performed in a timely manner to influence prescribing decisions? What is the minimum time for a CRP result to be available using point of care testing considering the average length of a primary care consultation?	Thank you for your comment. Recommendation 2 refers only to point of care testing. The trials considered in formulating this recommendation all used Point of Care (PoC) CRP testing. In primary care the prescribing decision is usually made with the patient at the index consultation and in order to influence this decision, results of CRP testing should be available within a reasonable timeframe. It is possible that using a laboratory based test may be possible however no trial included in this review examined remote CRP measurement. It is unclear whether a laboratory based test would be similarly effective and what delay in obtaining results would be both acceptable and effective. In order to implement this recommendation, PoC testing for CRP will need to be made available in primary care.
30		UK Clinical Pharmacy Association (UKCPA)	10	FULL	General	General	Although procalcitonin is reviewed, it is not referred to in the recommendations box in Table 16 (p75) 'linking evidence to recommendations - CRP and PCT for guiding prescribing decisions'.	Thank you for your comment. There was no good comparative evidence between CRP and PCT with regard to antibiotic prescribing. The GDG did not wish to

		Respiratory Group & Pharmacy Infection Network (PIN						make a specific positive or negative recommendation for PCT. The rationale for this is included in the evidence and link to recommendations table below the recommendation (Table 16, section 7.5, page 77).
26		UK Clinical Pharmacy Association (UKCPA) Respiratory Group & Pharmacy Infection Network (PIN	6	FULL	General	General	Consider including a recommended dose for all antibiotic recommendations throughout the guideline as part of antimicrobial stewardship. It is a common occurrence that low doses are prescribed rather than the doses recommended in national guidelines (e.g. BTS guidelines). This is partly due to prescribers referring to the advice in the British National Formulary. For example amoxicillin 250mg three times a day is often prescribed rather than the recommended dose of amoxicillin 500mg three times a day.	Thank you for your comment. Section 9.6.3.2 of the Guidelines Manual states "Readers are expected to refer to the summary of product characteristics (SPC) for details of dosages. Include dosage information only if there is evidence that a particular drug is often prescribed at the wrong dosage, or there is clear evidence about the effectiveness of different dose levels. …SPCs can be found in the Electronic Medicines Compendium." NICE guidelines do not duplicate information in the BNF and the BNF accessed electronically on 21 August 2014 says "By mouth, 500 mg every 8 hours, dose doubled in severe infection" As such, the GDG have not included dose in its recommendations.
21	SH	UK Clinical Pharmacy Association (UKCPA) Respiratory Group & Pharmacy Infection Network (PIN)	1	FULL	General	General	• With regards to terminology used by NICE in treatment guidelines to 'offer' or to 'consider' treatments, is generally appropriate. However in the context of antibiotic prescriptions, this terminology should place a greater emphasis that if prescribed, antibiotics must be taken and the course completed. 'Offer' suggests that antibiotics are optional and does not fit within the context of antimicrobial stewardship. Appropriate terminology should reflect that if antibiotics must be prescribed to treat pneumonia, and the course must be completed. Vague terminology is not	Thank you for your comment. The GDG acknowledges the importance of good antibiotic prescribing practice and communication with patients. The word "offer" is standard NICE terminology when there is good evidence supporting a treatment, and was therefore used in the wording of the recommendation.

							appropriate.	
22	SH	UK Clinical Pharmacy Association (UKCPA) Respiratory Group & Pharmacy Infection Network (PIN)	2	FULL	General	General	• Considering the length of the full guideline (441 pages), it is likely that most healthcare professionals will only read or refer to the shortened NICE guideline. Concern has been expressed that this is a very brief document and lacks detail. It has been suggested that the guideline committee consult the current BTS community acquired pneumonia guidelines (link) and the BSAC hospital acquired pneumonia guidelines (link) as these provide much more specific advice and recommendations. Specific consideration should be made to include: ○ Other diagnostic tests or biomarkers such as procalcitonin. ○ Specific antibiotic recommendations (first and second-line options) ○ Consideration of other supportive therapies - e.g. oxygen, fluids, VTE risk ○ Other markers of severity of pneumonia e.g. level of hypoxaemia, co-morbidities, multi-lobar pneumonia.	Thank you for your comment. NICE does not attempt to produce a textbook on a subject. All topics in the Pneumonia scope have been included in this guideline. To answer each point in turn: • Chapter 7 of the guideline considers CRP, procalcitonin and CXR as diagnostic tests, as per the scope. • First and second-line options were not specifically identified for systematic review in the scope. The GDG agreed that for pragmatic reasons, antibiotic classes would be compared, rather than specific antibiotics. Specific classes have been recommended for low-, moderate- and high-severity CAP. There was a paucity of evidence upon which to base recommendations for HAP and therefore the GDG recommended that local policies should be followed, based on knowledge of pathogen spectrum and the specific circumstances of the patient. • Other supportive therapies such as NIV and CPAP were considered, but no recommendations made due to paucity of evidence. When no recommendations are made, NICE expects that current practice continues. Fluid management is specifically excluded in the scope. VTE prevention is covered in other NICE guidance (CG 92).

								• The scope determined that severity assessment tools would be considered and compared. These tools include a composite of factors for assessment of severity. The GDG agreed that for pragmatic reasons it would not be possible to include single markers of severity in the systematic review.
23	SH	UK Clinical Pharmacy Association (UKCPA) Respiratory Group & Pharmacy Infection Network (PIN)	3	FULL	General	General	• Overall, the NICE guideline produces antibiotic recommendations that are rather vague. It would be useful if the recommendations were tightened, specifically with regards to (i) specific antibiotic to use for low, moderate and severe CAP, and for HAP (ii) dose of antibiotic (iii) formulation - oral or intravenous (iv) review duration for IV to oral switch (v) specific recommendations for identified pathogens	Thank you for your comments. To respond to each point: i) The GDG agreed that for pragmatic reasons, antibiotic classes would be compared, rather than specific antibiotics. Specific classes have been recommended for low-, moderate- and high-severity CAP. There was a paucity of evidence upon which to base recommendations for HAP and therefore the GDG recommended that local policies should be followed, based on knowledge of pathogen spectrum and the specific circumstances of the patient. ii) Section 9.6.3.2 of the Guidelines Manual states “Readers are expected to refer to the summary of product characteristics (SPC) for details of dosages. Include dosage information only if there is evidence that a particular drug is often prescribed at the wrong dosage, or there is clear evidence about the effectiveness of different dose levels. …SPCs can be found in the Electronic Medicines Compendium.” As such, the GDG cannot include dose in its recommendations.

								iii) Formulation was not identified as an area for review in the scope. Readers are expected to consult SmPCs for formulation advice. iv) Review for duration until switch was not agreed to be a priority by stakeholders at both the stakeholder workshop and after draft scope consultation. v) Management of pneumonia caused by specific identified pathogens is excluded in the scope (see section 4.3.2a).
58	SH	Aspire	2	FULL	General	General	Reference to the recommended use of azithromycin when *Legionella* is suspected/confirmed has not been included in the guidelines. This recommendation was made in the British thoracic society (2009) and European respiratory society (2011) guidelines. (Lim et al, 2009) (Woodhead et al, 2011)	Thank you for your comment. The scope excludes the management of specific pathogens.
2	SH	Cempra Pharmaceuticals, Inc.	1	FULL	General	General	We appreciate the opportunity to review the draft guidance “Pneumonia: diagnosis and management of community- and hospital-acquired pneumonia in adults”. This document provides a very useful review of the literature that supports sound, clinically relevant evidence-based guidance for the management of community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP). We would to comment on two particular aspects of the document; first, the recommendation that outpatient pneumonia of low severity be treated with single drug therapy (optimally, amoxicillin), and second, the role of biomarkers (specifically CRP) in CABP treatment decision making. In two ongoing, double-blind, prospective, comparative clinical trials to evaluate a new macrolide antibiotic for treatment of community-	Thank you for your comment and support of the recommendation. In response to your first point: NICE does not include data from ongoing trials. The GDG considered all studies matching their pre-agreed protocols, which included patients who may have had pneumonia caused by any pathogen - the objective being to determine the most cost-effective empirical antibiotic choice given that at presentation the causative organism is not yet identified. The GDG reiterates, on balance, their recommendation.

							acquired bacterial pneumonia (CABP) in adults (SOLITAIRE-ORAL and SOLITAIRE-IV), we have employed multiple diagnostic methods to arrive at an etiological diagnosis. This has included Mycoplasma pneumoniae culture from pharyngeal swabs in all patients enrolled. Strikingly, M. pneumoniae has been detected in approximately 8% of all patients enrolled to date. In the majority of these cases, M. pneumoniae was the sole pathogen identified. These patients have presented with significant radiographically confirmed pneumonia (with baseline plasma CRP levels ranging from 15-284 mg/L, and only a minority with < 20 mg/L assay results). Thus, while we well recognize that the rising prevalence of pneumococcal resistance to 1st and 2nd generation macrolide antibiotics has led to the preferred use of beta-lactam antibiotics as first line therapy, we offer, simultaneously, the caution that 'atypical pathogens' (Mycoplasma, Chlamydia, Legionella) have been and remain significant contributors to CABP incidence. These genera are not appropriately treated with beta-lactam antibiotics, and in circumstances where monotherapy is recommended, a cautionary note to be mindful of the potential role of the 'atypical pathogens' is warranted. With regard to the proposed role of CRP testing in clinical treatment decision, we believe that further discussion is warranted. CRP, similar to erythrocyte sedimentation rate (ESR) is a sensitive, but non-specific acute-phase-reactant protein. Data from numerous studies demonstrate that plasma CRP level is an excellent marker of systemic inflammation and is generally greater in bacterial compared to viral infections. Recently, plasma procalcitonin (PCT) has been demonstrated in numerous studies to have a	In response to your second point, thank-you for supporting our view that CRP testing may be a useful adjunct to good clinical assessment. The studies you quote were not included in our review as they didn't match our review protocol (Hopstaken et al ,2003 was a diagnostic study, Andre et al 2004 had a different study design and population from the one set up in the review protocol and the Melbye 1995 study was not published in English). The GDG acknowledges that cut-points for CRP concentrations may be open to later modification, but considers the levels set in this guidance to be based on the best evidence available.

							similar if not superior potential utility as a biomarker for the severity of pneumonia upon presentation, and as a tool for decision making regarding therapy. However, we note that the Draft Guidance Document appropriately indicates that these data, when available, should be considered supportive or ancillary to clinical judgment, and we couldn't agree more. Several studies were cited in the document that provide the evidence base for a CRP threshold of 20 mg/l (as a threshold for antibiotic treatment), but upon review, only two studies were designed to determine this breakpoint. Other studies, subsequent to these, were actually confirmatory in design, since a breakpoint of 20 mg/l was selected as the breakpoint a priori. Hopstaken, et al. [2003] conducted a cross-sectional design study of patients with lower respiratory tract infection (LRTI) seen at 15 medical practices between January 1998 and April 1999 in the Netherlands. Sensitivity and specificity analyses of the data for the 246 LRTI patients showed that CRP and ESR were increased in 97% of patients with pneumonia. The overall diagnostic performance of CRP was better than ESR (p=0.02). An algorithm based on presence of diarrhea, dry cough, temperature ≥38°C, and CRP was used to define the probability of pneumonia. Patients with a maximum of 1 positive score from among diarrhea, dry cough, temperature ≥38°C, and a CRP<20 defined a group of "low-risk" patients (n=107). Using a CRP breakpoint of 20, the authors determined that antibiotic administration would have been avoided in 80 of the 193 patients who received antibiotics, resulting in a 2.5% risk of missing a true pneumonia (defined as an infiltrate on a chest x-ray obtained 3 days after presumptive diagnosis).	

							When the near-patient (point of care) CRP test was introduced in Scandinavian countries, there was an expectation that inappropriate antibiotic use (i.e. prescribing for upper respiratory tract infection (URI) or viral respiratory infection) would decrease, but several studies have shown that this was not the case. Although the CRP was considered a sensitive indicator of LRTI, the ability to use CRP in the management of patients to identify those who required antibiotic therapy was not resolved. Therefore, André, et al. [2004] conducted a prospective study in 5 counties in Sweden during 1 week in November 2000 and 2002, to assess the use of CRP in relation to duration of symptoms and antibiotic prescribing in patients with LRTI. Most of the CRP tests were by one of two point of care tests; NycoCard® CRP Single Test, Axis-Shield PoC AS (40%), and QuickRead CRP, Orion Diagnostica (50%). A CRP was not a required test for this study. Among the 6778 consultations for patients presenting with any respiratory tract infection (RTI), a decision to obtain a CRP was at the discretion of the healthcare provider. CRP was obtained in 42% of the cases, most often when the presenting diagnosis was pneumonia, atypical pneumonia, unspecified respiratory infection and acute bronchitis, and was done more frequently for older patients, patients with longer duration of symptoms, and patients returning for a revisit ($p < 0.001$). A total of 50% of CRP results were <10 mg/l, 17% were ≥50 mg/l, and 7% were ≥ 100 mg/l. As expected, increased CRP was found more often among patients with a diagnosis of pneumonia in comparison with patients with pharyngitis, bronchitis, and other URI. In this study, when CRP was used, 41% of patients were treated with antibiotics compared to 44% of patients when a CRP was not obtained. Although statistically	

							significant (p<0.01), the overall impact of CRP was considered to be minor. If one applied a CRP breakpoint to rule out pneumonia of < 25 mg/l (similar to that used by Hopstaken), 34% of all patients with a diagnosis of LRTI were prescribed antibiotics. The large number of low CRP values indicated that the test was used to rule out serious diseases. Most GPs prescribed antibiotics when the CRP ≥25, a value derived from studies done in hospitalized patients and experimental conditions in the early 1980s. In those studies, a value <20 mg/l was considered normal or slightly elevated, 20-39 mg/l was increased, often associated with a viral infection and difficult to interpret, 40-99 mg/l significantly increased usually due to bacterial infection, and >100 mg/l almost always associated with bacterial infection. Those breakpoints were challenged in subsequent studies as it has only a modest predictive power (PP) (0.43) in suspected pneumonia patients, decreasing to a PP=0.12 in all RTI (Melbye, 1995). The authors also noted that the utility, namely "does the test distinguish between patients with and without pneumonia?" was not addressed prior to licensure of the point of care CRP test. A CRP breakpoint of 20 mg/l was used by Cals, et al. in subsequent studies which comprise much of the data for the current draft guidance. We anticipate that the implementation of the C-reactive protein (CRP) thresholds for antibiotic administration (withhold if <20 mg/l, possibly delay if between 20 and 100 mg/l), and administer if >100 mg/l) will result in delayed treatment of a measurable percentage of patients with a clinically relevant bacterial pneumonia who should be treated with antibiotics. In our two ongoing, double-blind, prospective, comparative clinical trials identified above, among	

							several diagnostic tests we have included in the trials, we have assayed baseline CRP using a high sensitivity latex immunoturbidimetry CRP assay, performed in a central laboratory. The results from these trials will be published when completed, but we are pleased to share some of the diagnostic data collected thus far. To date, one third of patients identified with Legionella infection would have fallen into the 'delay therapy' group. While all patients with pneumococcal bacteraemia had elevated CRP levels (above the 'treat immediately' threshold), others with fever, leukocytosis, hypoxia, and isolation of pneumococcus from sputum fell into all three categories (do not treat, possibly delay treatment, and treat immediately). All of these patients had elevated CRP, but not all had concentrations >20 mg/l or >100 mg/l. Accordingly, we support the message that CRP testing, while useful, should be considered ancillary, and that these biomarker assays should not substitute for the sound clinical judgment of care providers. We would be pleased to meet with the committee developing this guidance to share our data in greater depth.	
6	SH	British Thoracic Society	4	FULL	General	General	No recommendations are made regarding the need (or lack of) to test for underlying immunodeficiency eg HIV testing	Thank you for your comment. The Guideline scope, developed in consultation with Stakeholders, excludes consideration of conditions which might pre-dispose to pneumonia, including HIV infection. No systematic review was performed and no recommendations can be made.
7	SH	British Thoracic Society	5	FULL	General	General	The style of presentation follows other NICE guidance but is difficult for the reader. An introduction to the style of presentation may be useful.	Thank you for your comment. Formatting is determined by NICE. Sections 2 and 3 in the guideline explain how the reader can effectively navigate the guidance, and section 5 explains the methods used and how the evidence is presented.

11	SH	Royal College of Physicians of Edinburgh.	1	FULL	General	General	The College has sought expert comment on the guideline which at 444 pages long is extensive and appears to be a sensible guideline for the management of pneumonia; all the recommendations are backed up by tables of papers and areas of doubt are acknowledged.	Thank you for your comment.
13	SH	British Geriatric Society	1	FULL	General	General	The guideline is well written, and we agree with the recommendations that have been proposed. Pneumonia is a very common cause of illness in the older adult and we note you have made reference to the vague presentation in older adults in your introduction. The lack of symptoms and signs in older adults should rightly be emphasized, as opportunities to treat early may be missed. Many patients admitted with pneumonia are older, frail and require a comprehensive and rapid multidisciplinary assessment and management plan. We understand the document is not examining palliative situations. We feel it is of the utmost importance not to fall into the trap of previous guidelines which have focused purely on a single condition approach, with an assessment of disease severity, and which state which antibiotics should be given - in practice most Trusts use CURB65 and have their own formularies based on local policies to reduce C.difficile . There is a golden opportunity to highlight the importance of a comprehensive assessment of the older person (see suggestions listed below). While it could be claimed that this applies equally to many conditions, it is the case that pneumonia is one of the commonest causes for admission of older adults and a major healthcare challenge and	Thank you for your comment. Section 4.1.1c) of the scope, developed after consultation with Stakeholders, states that “No patient subgroups have been identified as needing specific consideration.” We looked for evidence specific to elderly populations. We found very little, but it is important to emphasise that the average age of the subjects in most of the studies was high, because pneumonia is much commoner in the elderly. In other words, all the Recommendations very much reflect best management of pneumonia in the elderly. There was a care of the elderly physician on the Group (indeed there were 2 for some of the time) who contributed fully to deriving the recommendations. We have added detail about frail elderly patients to the safe discharge linking evidence to recommendations section. This is a guideline for a single condition as determined by the remit from the Department of Health and the scope. For all review questions, the GDG considered studies which included older people when available. The studies

							these guidelines could highlight to General Physicians the relevance of an approach that goes beyond just assessing the chest. We therefore make 3 suggestions that may contribute to the overall guideline:	included in the severity assessment review used all patients presenting, including older people and those with comorbidities. The recommendations in this guidance are therefore relevant to this population. The GDG would expect an overall clinical assessment of the older person to be part of the consultation, but it is beyond the scope of this guideline to perform a specific analysis of and produce recommendations for this.
14	SH	British Geriatric Society	2	FULL	General	General	There is no mention in the document about the relevance of possible aspiration as a cause of "community acquired" pneumonia. It may be that the GDG felt this was outside their scope but it is the case that many older adults present with pneumonia initially felt to be community acquired. We feel a statement concerning the prudence of considering a swallow assessment in older adults and those with stroke and other risk factors for dysphagia would be worthwhile – this article highlights the importance of this issue- Cabre M, Serra-Prat M, Palomera E, Almirall J, Pallares R, Clave P. Prevalence and prognostic implications of dysphagia in elderly patients with pneumonia. Age Ageing. 2010;39:39–45.	Thank you for your comment. We did not prioritise this within the scope.
18	SH	NHS England	2	FULL	General	General	I don't like the instruction to consider a delayed antibiotic prescription inpatients with equivocal CRP level. I think this is a safety issue and could lead to delayed treatment if the timing of the test is not current or if the pneumonia worsens rapidly. This is the area where the doctor has to use his clinical judgement. Any algorithm here is risky.	Thank you for your comment. The GDG is not advocating delayed prescription for patients with a clear clinical diagnosis of pneumonia, or with CXR-confirmed pneumonia. The GDG has changed the • wording of the CRP recommendation to highlight that the recommendation is only applicable in instances in which a diagnosis of pneumonia has not been made, and • heading to the CRP recommendation ("Presentation with

								symptoms of lower respiratory tract infection") in order to further emphasize that only patients with symptoms which raise the possibility of pneumonia but in whom there is uncertainty about the need for antibiotics are considered for CRP testing (i.e. those with clinically suspected pneumonia should receive antibiotics as soon as possible, and those thought clinically to have a self-limiting RTI should receive no antibiotic therapy). • the subheadings in the full list of recommendations to clarify specific management aspects of LRTI, CAP (low-, moderate- and high-severity) and HAP. The GDG considered the use of CRP as a point of care test within the community. Detailed explanations about the necessary considerations in order to maximise outcomes have been included in the evidence and link to recommendations in Table 16, section 7.5, page 77. The CRP recommendation now allows a more sophisticated approach to risk stratification in people with clinically undetected pneumonia than is currently possible. Finally, the GDG note that NICE Guideline CG69 (LRTI) currently recommends a delayed antibiotic prescription.

19	SH	NHS England	3	FULL	General	General	There is no reference to atypical presentations of pneumonia where other features (foreign travel, occupation, bird exposure, headache, diarrhoea etc) may point the way to a CXR in patient who don't have classical features of pneumonia.	Thank you for your comment. The Scope of the Guideline did not include an analysis of symptoms of pneumonia, nor did it include risk factors for atypical pneumonia. The only diagnostic issue prioritised during scoping was the role of CRP & procalcitonin.
36	SH	Department of Health	1	FULL	General	General	Thank you for the opportunity to comment on the draft for the above clinical guideline. I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation	Thank you for your comment.
38	SH	Royal College of Nursing	1	FULL	General	General	I have read the draft and have no comments it seems all good to me.	Thank you for your comment.
39	SH	West of Scotland Specialist Virology Centre	1	FULL	General	General	Lack of recommendations regarding sample testing for virology and microbiology. There are now many studies confirming the importance of viruses in the aetiology of both moderate and severe pneumonia. Indeed locally every year we see numerous hospital admissions associated with severe viral RTI and neg microbiology. Access to full resp viral testing is patchy across the UK. Similarly, depending on the frequency of these guidelines, molecular testing for bacterial pathogens is likely to be adopted over the next few years	Thank you for your comment. Virology testing was not prioritised for review in the scope and hence was not included in the microbiology question. The GDG acknowledges that molecular testing may be adopted in the future.
40	SH	West of Scotland Specialist Virology Centre	2	FULL	General	General	Use of urinary antigen tests is worrying, they have low sensitivity and in the case of Legionella may miss non pneumophila types. The use of pneumococcal Ag testing in urine is v. insensitive	Thank you for your comment. The recommendation is not made for urinary antigen tests to be used in isolation. The GDG included high-quality valid studies of pneumococcal and legionella sensitivity and specificity. The GDG acknowledges the limitations of the test but considers that there is still a role for them.
41	SH	West of Scotland Specialist	3	FULL	General	General	Use of neuraminidase inhibitors empirically. currently their use is recommended by PHE, if the BTS disagrees with this it might be worth including	Thank you for your comment. Use of neuraminidase inhibitors was not part of the scope for this guideline and therefore

		Virology Centre					an explanation	the Guideline does not comment on them. This does not mean that the GDG disagrees with their use. Also please note, this is a NICE guideline, not a BTS guideline.
35		UK Clinical Pharmacy Association (UKCPA) Respiratory Group & Pharmacy Infection Network (PIN	15	FULL	General	General	It would be useful if the guideline gave more detail regarding treatment of pneumonia in patients with penicillin allergy. It gives recommendations for mild CAP, but does not go into any detail for moderate/severe CAP and HAP. Dealing with patients who have reported / suspected beta-lactam allergy is a common occurrence.	Thank you for your comment. The GDG considered a recommendation in low-severity CAP for patients with penicillin allergy to be reasonable because there was evidence that a tetracycline or macrolide are effective for low-severity CAP. However, for moderate- to high-severity CAP, the evidence was less convincing and the GDG refrained from making a specific recommendation. In this circumstance current practice is presumed to be upheld and it is expected that local policies for patients with allergy would be followed. The linking evidence to recommendations table (Table 101, page 265) has been expanded to suggest that clinicians should liaise with local microbiology services to ensure adequate empirical cover for common pathogens for patients with moderate-severity community-acquired pneumonia who are allergic to penicillin when an alternative is not clear.
7		UK Clinical Pharmacy Association (UKCPA) Respiratory Group & Pharmacy	7	FULL	General	General	Consider inclusion of recommended route (IV or oral) for antibiotics, or whether this should be guided by local formularies, local pathogens and clinical circumstances.	Thank you for your comment. Recommended route was not identified as an area for systematic review in the scope, and in any case would vary with antibiotic and with clinical circumstances. Readers are expected to consult SmPCs for formulation advice.

		Infection Network (PIN)						
29		UK Clinical Pharmacy Association (UKCPA) Respiratory Group & Pharmacy Infection Network (PIN	9	FULL	General	General	Antimicrobial management of HAP is entirely unhelpful. Consider inclusion of recommended first and second-line antibiotics, doses and durations for specific bacterial causes.	Thank you for your comment. NICE Guidance is based on best available evidence, and as the Full Guideline shows, there is very little evidence available to guide recommendations in HAP. Nevertheless, the GDG discussed antimicrobial management of HAP at length, and in the absence of evidence and because of possibility of different causes with different antibiotic resistance patterns in different hospitals and different patient populations, the group felt that it was not feasible to include first- and second-line antibiotics for HAP. With regard to specifying doses and durations, Section 9.6.3.2 of the Guidelines Manual states “Readers are expected to refer to the summary of product characteristics (SPC) for details of dosages. Include dosage information only if there is evidence that a particular drug is often prescribed at the wrong dosage, or there is clear evidence about the effectiveness of different dose levels. …SPCs can be found in the Electronic Medicines Compendium.” With regards to management of specific bacteria, treatment for specific pathogens is an exclusion in the scope.
25		UK Clinical Pharmacy Association (UKCPA) Respiratory	5	FULL	General	General	The evidence does not support the conclusion that antibiotics should be given within 4 hours. This seems reasonable for moderate to severe pneumonia, but not non-severe (CURB 0-1) as this could be treated in community and we would	Thank you for your comment. The GDG debated this issue at length. There is no time recommendation for patients presenting outside hospital. For patients presenting to or in hospital with

		Group & Pharmacy Infection Network (PIN					certainly not be asking GPs to see patients and ensure they have been administered antibiotics within a 4 hour window.	moderate- to high-severity CAP, the GDG agreed that the evidence supports a recommendation to give antibiotic therapy within 4 hours of presentation at hospital.
65	SH	Healthcare Improvement Scotland	1	General	General		We agree with the antibiotic choices in general and the recommendation for 5 days of treatment of non-severe/ low risk CAP and HAP.	Thank you for your comment.
66	SH	Healthcare Improvement Scotland	2	General	General		No recommendation is made for antibiotic choice for mod-severe CAP with pen/ beta lactam allergy. Interpret this to mean there is limited evidence and it should be for local decision	Thank you for your comment. Your interpretation is correct. The GDG considered a recommendation in low-severity CAP for patients with penicillin allergy to be reasonable because there was evidence that a tetracycline or macrolide are effective for low-severity CAP. However, for moderate- to high-severity CAP, the evidence was less convincing and the GDG refrained from making a specific recommendation. In this circumstance current practice is presumed to be upheld and it is expected that local policies for patients with allergy would be followed. The linking evidence to recommendations table (Table 101, page 265) has been expanded to suggest that clinicians should liaise with local microbiology services to ensure adequate empirical cover for common pathogens for patients with moderate-severity community-acquired pneumonia who are allergic to penicillin when an alternative is not clear.
63	SH	British Infection	1	Full	General	General	It would be helpful if the guidance were to state that the previous microbiological history of the	Thank you for your comment. Management in patients with underlying

		Society					patient should be taken into account when considering empirical antibiotic treatment. This is particularly important for those patients who have chronic respiratory conditions in whom resistant bacteria become selected.	chronic respiratory conditions, in whom recent microbiological results would be available, was not prioritised in the Scoping process. No evidence was examined and therefore no recommendations can be made.
64	SH	British Infection Society	2	Full	General	General	There is discussion about near patient testing of C Reactive Protein (CRP) but no clear advice is given. The argument against is cost. We believe that the guidance should "get off the fence" and state whether it advises this, on evidence base, or whether it does not. If further research is required then it should say this. If the guidance remains non-committal on this issue, there may be commercial pressure brought to bear on GPs and others with references to NICE guidance.	Thank you for your comment. The GDG has been as precise as possible, based on the evidence.
20	SH	NHS England	4	FULL	Glossary	8	In the glossary on page 8 of the abbreviated guideline a diagnosis lower respiratory tract infection should be made by the absence of pneumonia on the CXR.	Thank you for your comment. The GDG took a different view. The term lower respiratory tract infection includes pneumonia along with other respiratory infections and this has been further explained in the "terms used in this guideline" section in both the full and NICE versions of the guideline.
3	SH	British Thoracic Society	1	FULL	4.5	22	No comments are made on follow-up after hospital discharge, including investigations. This seems an unusual omission, especially when a key (useful) feature is the provision of specified patient information, which partly aims to reduce healthcare usage and consultation, yet does not address how/when a patient should reconsult. This is particularly problematic as this guidance will clearly replace the BTS 2009 guideline, which includes the recommendation for a follow up at 6 weeks. Since this guideline does not address that statement, neither explicitly removing it, nor updating or revising it, this leaves providers and commissioners in an ambiguous situation.	Thank you for your comment. Follow-up after hospital discharge and investigations after discharge were excluded in the scope after public consultation with stakeholders (section 4.3.2f) of the scope). The GDG sought evidence about how/when a patient should consult, but no evidence meeting the pre-specified protocol was identified, and agreed that no recommendation should be made in the absence of evidence.

								NICE prioritises for systematic review areas of poor or inequitable practice, or areas where there is uncertainty. Where NICE guidance does not address specific topics, it is assumed that current practice continues.
4	SH	British Thoracic Society	2	FULL	4.5	22	It is unclear why other management strategies have also been excluded from the guidelines such as the use of statins.	Thank you for your comment. NICE guidance is not intended to be a textbook covering all areas of possible relevance. Rather, the guidance is based on prioritisation of topics for systematic review in consultation with stakeholders and a scope determined early in development. Statins (amongst other topics) were not prioritised in the scope (section 4.3.2d)
48	Alere	Alere	7	FULL	6.1	49, lines 10-11	We repeat our comment no. 3 above.	Thank you for your comment. Since there is no accepted definition of clinical judgement and because the GDG did not examine studies' use of clinical assessment, the GDG does not consider it possible to discuss this further.
46	Alere	Alere	5	FULL	6.1	49	We repeat our comment no. 1 above.	Thank you for your comment. Since there is no accepted definition of clinical judgement and because the GDG did not examine studies' use of clinical assessment, the GDG does not consider it possible to discuss this further. The GDG has also altered the subheadings in the full list of recommendations to clarify management of patients with LRTI, CAP (low-, moderate- and high-severity) and HAP. The scope of the guideline did not include an analysis of symptoms or examination findings in pneumonia. Even

								if we had sought this, we suspect that hard evidence analysing these features would not exist since they have been an accepted part of clinical practice for so long. We are therefore not able to produce a statement on the evidence-based aspects of clinical assessment".
47	Alere	Alere	6	FULL	6.1	49, lines 9-12	We repeat our comment no. 2 above.	Thank you for your comments. The GDG feels that the strength of the recommendation reflects the level of evidence.
60	SH	Aspire	4	FULL	6.2 point 16 & 17	52	In this section the following statement is written: '*16. consider dual antibiotic therapy with amoxicillin and a macrolide (such as clarithromycin) for patients with moderate-severity community-acquired pneumonia* *17. consider dual antibiotic therapy with a beta-lactamase stable beta-lactam (such as co-amoxiclav) and a macrolide (such as clarithromycin) for patients with high-severity community-acquired pneumonia'* We believe that azithromycin should be used instead of clarithromycin as a first line therapy in combination with amoxicillin, however we do accept that due to the different requirements/ risks associated with each patient, that the recommendation might also state 'such as azithromycin or clarithromycin'. Our reasons are as follows: ***Differential selection of macrolide resistance*** A randomised, double-blind, placebo-controlled study of the effect of azithromycin (500 mg once daily for 3 days) and clarithromycin (500 mg twice daily for 7 days), was measured against placebo in four groups of volunteers by use of oral	Thank you for your comments. In the light of your comments, the GDG has reconsidered whether clarithromycin should be included as a named example, and have decided that all examples should be removed from the recommendation. The Malhotra-Kumar paper was not included because it is not a paper about pneumonia (healthy volunteers were assessed).

							streptococci as model organisms (Malhotra-Kumar et al, 2007). A clearly defined effect on commensal pharyngeal streptococci was observed, with both drugs selecting for macrolide resistance. Although azithromycin quantitatively selected for resistance, clarithromycin qualitatively selected for the higher resistance-conferring *erm(B)* gene. The acquisition of *erm(B)* represents a more efficient resistance mechanism for the organism. Not only does it confer increased resistance to the macrolide group of antibiotics, but it also induces resistance to the lincosamide, streptogramin B, and tetracycline groups. This poses a heightened risk to public health. (Dancer, 2007) *Interaction with other drugs* A significant advantage of azithromycin over clarithromycin that appears to have been overlooked is its smaller range of interactions with other drugs. Clarithromycin has been reported to interact with CYP3A4 enzymes, which results in decreased clearance of other agents whereas azithromycin interacts poorly with CYP3A4 system. (Abu-Gharbieh et al, 2004) (Owens and Nolin, 2006). This means that therapeutic monitoring is required for concomitant medication. According to the Zedbac SmPC, azithromycin interacts with ciclosporin, digoxin, ergot derivatives, warfarin and terfenadine. The SmPC for Klaricid IV shows interaction with 27 different drug/classes, including all of the aforementioned and benzodiazepines metabolised by CYP3A, tolterodine, ritonavir and antiarrhythmics. CAP is common in the elderly who are likely to take a variety of medication. (Zuckerman, 2004). It has been reported that clarithromycin has a significant effect on atorvastatin pharmacokinetic parameters, while there is no interaction between atorvastatin and	

							azithromycin. When co-administered, clarithromycin raised subject exposure (AUC24) by 82% and peak plasma concentrations by 56%. The data suggest that while azithromycin appears to be safe to co-administer with atorvastatin, clarithromycin should be avoided in patients taking this and similarly metabolized HMG-CoA inhibitors. (Amsden et al, 2002) Azithromycin IV has a number of potential benefits over clarithromycin, and fewer contraindications, making it the more suitable macrolide antibiotic as a first line treatment. It is less cardiotoxic than clarithromycin, has better infusion site tolerability (Zimmermann, 2001) and the risks of hepatotoxicity are comparable between clarithromycin and azithromycin. There is no evidence to support the use of clarithromycin in preference to azithromycin, By contrast, the reduced risks of using azithromycin as a first line treatment are well evidenced in terms of: its effects on *Legionella*, a decreased risk of inducing cross-resistance to other antibiotic groups ,a lower incidence of adverse interactions with other medications, in particular statins, and higher likelihood of patient completion of treatment courses due to lower dosing rates and treatment times.	
17	SH	NHS England	1	FULL	7		There is no reference to the chest X-ray in the diagnostic section. It may be that the authors think that this is so obvious that they do not need to include it. However, the BTS care bundle contains the ambition to have had a reported Chest X ray within four hours. I think that any patient admitted to hospital with a suspicion of pneumonia should have a good quality reported X ray as soon as possible. This ensures that the diagnosis is correct.	Thank you for your comment. The GDG acknowledges that CXR is the gold standard diagnostic test for pneumonia in the general introduction on pages 14 and 15, and in the introduction to the diagnostic tests chapter on page 55. The developers have added a sentence to the “terms used in this guideline” for both CAP and HAP in the NICE version to highlight that CXR is required to make a

								definitive diagnosis. Recommendation 9 has been amended to further strengthen the role of X-rays: ***Put in place processes to allow diagnosis (<u>including X-rays</u>) and treatment of community-acquired pneumonia within 4 hours of presentation to hospital***, supports the principle referred to in the BTS care bundle. However, care bundles and timing of X-rays for diagnostic purposes were not prioritised by the GDG or stakeholders during scope consultation and hence recommendations pertaining to these subjects cannot be made.
49	Alere	Alere	8	FULL	7	55, lines 17-26	We would like to point out that C-reactive protein POCT is a quick finger stick blood test, which has been specifically designed for primary care. A C-reactive protein test can (i) reassure both patients and GPs about the diagnosis as well as the recommended course of treatment, and (ii) is easy to implement in a primary care setting: (i) Several published studies show that a CRP POCT significantly reduced antibiotic use in patients with RTIs presenting to GP practices and that a C-reactive protein point of care testing result helps to facilitate the discussion around whether an antibiotic is necessary and reassures patients with no impact on patient safety. In addition, it has been demonstrated to improve patient experience of the consultation (Little P *et al*. 2013; Bjerrum L *et al*. 2011; Cals JWL *et al*. 2009; Cals JW *et al*. 2013; Coenen S. 2012). C-reactive protein POCT is used to discriminate severity of infection and extent of inflammation. It is not used to diagnose bacterial vs. viral infection,	Thank you for your comment. The GDG took into account the data from Little P *et al*. 2013; Cals JWL *et al*. 2009; and Cals JW *et al*. 2013. Coenen S. 2012 was not picked up in our search because it was a narrative summary and Bjerrum L *et al*. 2011 was excluded as it was an audit and did not meet pre-specified protocol criteria for inclusion in the systematic review. The GDG was aware of the other points you make and these considerations helped to inform the recommendation they made.

							but it does help to decrease diagnostic uncertainty, and can help reassure both patient and clinician as to the most appropriate course of treatment (Verheij ThJM *et al*. 2011). (ii) A C-reactive protein POCT is very easy to run and does not require technical complex training. It takes just 4 minutes to achieve a quantitative result. POCT in primary care is widespread in the UK. For example, approximately 2500 POCT instruments are already installed in GP practices for the purpose of the NHS Health Check programme (lipids and HbA1c levels). C-reactive protein POCT would be a simple addition and could be conducted by practice nurses, as is already the case in many European countries.	
50	Alere	Alere	9	FULL	7.2	56 line 4 onwards	We would like to draw the Guideline Development Group's attention to the following recently-published paper, which we feel merits consideration: Andreeva E. Melbye H. Usefulness of C-reactive protein testing in acute cough/respiratory tract infection: an open cluster-randomized clinical trial with C-reactive protein testing in the intervention group. *BMC family practice* 2014; 15: 80).	Thank you for your comment. The Andreeva E. Melbye publication fallsoutside the cut-off date for this guideline.
51	Alere	Alere	10	FULL	7.3	71	We note that the NCGC used the Oppong paper to inform the development of its own cost analysis (Oppong R. 2013). We also note that it reviewed one published cost-utility analysis comparing C-reactive protein POCT with clinical judgement alone, but had some concerns about its applicability to an NHS population.	Thank you for your comment. The guideline recommendations are based upon published evidence where this is available. Thank you for providing this information and whilst we cannot include it, it is helpful to know about it.
53	Alere	Alere	12	FULL	7.3,	72, line 3	As a consequence of the wrong figure being included in Table 12, the results of the incremental	Thank you for your comment. The cost of the test reported in the guideline includes

					Table 13		cost-effectiveness analysis in Table 13 are also incorrect.	the cost of the staff time to perform the test, equipment and other considerations and we have added a sentence to the full guideline to clarify this. Therefore the GDG does not believe the figure in the guideline requires adjustment.
54	Alere	Alere	13	FULL	7.3, Table 15	74, line 4	The unit cost of a C-reactive protein POCT is £4.19, not £12-15 as suggested by the Guideline Development Group.	Thank you for your comment. The cost of the test reported in the guideline includes the cost of the staff time to perform the test, equipment and other considerations and we have added a sentence to the full guideline to clarify this. Therefore the GDG does not believe the figure in the guideline requires adjustment.
52	Alere	Alere	11	FULL	7.3, Table 12	71, lines 25 & 26	The cost of the C-reactive protein test including equipment given in Table 12 is inflated. A single C-reactive protein test, including quality control features, costs £5.53 per test (comprising £4.19 for the unit cost of the test plus £1.34 for the depreciation of the instrument on a per test basis).	Thank you for your comment. The cost of the test reported in the guideline includes the cost of the staff time to perform the test, equipment and other considerations and we have added a sentence to the full guideline to clarify this. Therefore the GDG does not believe the figure in the guideline requires adjustment.
56	Alere	Alere	15	FULL	7.5, Table 16	78	In the section marked “other considerations” we note the Guideline Development Group’s observation that UK healthcare professionals are already familiar with C-reactive protein testing due to its widespread laboratory use, and that this may result in less training being required for its implementation as a POCT. We would like to make the following points: • C-reactive protein POCT is a quick finger stick blood test, specifically designed for primary care. It is quick, simple and easy to use. A study showed CRP testing to have little effect on GP workload in 50% of practices (Cals JW *et al*. 2010a).	Thank you for your comments. The GDG was aware of the other points you make and these considerations helped to inform the recommendation they made.

							• The test is very easy to run and does not require technical or complex training to undertake. It takes just 4 minutes to achieve a quantitative result. • In other European countries, the test is frequently run by practice nurses, similar to how Healthcheck tests for lipids and HbA1c are carried out in primary care practices in England. The prescribing decision would still rest with the GP, based on his or her clinical assessment of the patient. • POCT in primary care is widespread in the UK. For example, approximately 2500 POCT instruments are already installed in GP practices for the purpose of the NHS Health Check programme (lipids and HbA1c levels). C-reactive protein testing would be a simple addition and could be conducted by practice nurses, as is already the case in many European countries.	
55	Alere	Alere	14	FULL	7.5, Table 16	76, line 8	We note the Guideline Development Group's concern that a recommendation for C-reactive protein POCT with four different groups and four different management options might be considered too complicated and difficult to implement. We reiterate our suggestion that a simple algorithm should be incorporated into the final guideline (see comment 1 above). POCT in primary care is widespread in the UK. For example, approximately 2500 POCT instruments are already installed in GP practices for the purpose of the NHS Health Check programme (lipids and HbA1c levels). C-reactive protein testing would be a simple addition and could be conducted by practice nurses, as is already the case in many European countries.	Thank you for your comment. The GDG has debated the use of an algorithm at length and concluded that an algorithm cannot adequately capture the nuances of both the recommendation and the overlap with CG69.
15	SH	British	3	FULL	8.7		Delirium: In assessing severity of pneumonia, both	Thank you for your comment. This goes

		Geriatric Society					in the community setting and in hospital the guideline rightly highlights the importance of "confusion" and recommends the use of CRB-65 or CURB-65. We would like to highlight the importance of a proper cognitive assessment. Delirium or confusion has the highest weighting in the CURB scores and delirium carries a two fold increased mortality in hospitalised inpatients generally. We would propose that the pneumonia assessment, is married up to NICE guidelines on delirium [CG103] and that a basic assessment of cognitive function is carried out e.g. Abbreviated Mental Test score 10 or the Confusion Assessment Method as advocated in NICE CG103. Otherwise "confusion" will be missed and severity underestimated. Appropriate steps to reduce delirium can then be taken such as ensuring adequate oxygenation, orientation and avoiding inappropriate ward moves.	beyond the scope of the guideline. The studies of CURB65 and CRB65 used the abbreviated mental test score, so it is on this evidence that the GDG has based the recommendation. However we have added a footnote to Box 2 Bullet Point 1 directing readers to the NICE guideline on delirium.
5	SH	British Thoracic Society	3	FULL	10.2.4	169	The GDG felt that it was also desirable for antibiotics to be commenced as soon as reasonably possible for patients with CAP treated outside hospital. It is not clear how to manage this statement with the guidance 7.5 pg 75 which suggest the use of a CRP test and to consider a delayed antibiotic prescription (a prescription for use at a later date if symptoms worsen) if the C-reactive protein concentration is between 20 mg/litre and 100 mg/litre. Some clarity and connection between the 2 statements should be made.	Thank you for your comment. The recommendations refer to two mutually exclusive groups of patients. The GDG agreed that antibiotic therapy should be commenced as soon as possible for those with a clinical diagnosis of pneumonia. The recommendation for CRP + delayed antibiotic therapy is relevant in those where there is uncertainty about the need for antibiotics.
61	SH	Aspire	5	FULL	10.8.4 Table 100	262	In this section the following statement is written: '*For the macrolide component, the GDG felt that wide clinical experience supported the use of clarithromycin as a first choice - erythromycin is more poorly tolerated due to gastrointestinal side effects'*	Thank you for your comments. Azithromycin was considered, but experience in the UK is not as wide as with clarithromycin for the treatment of pneumonia. The LETR has been amended to reflect this, and examples from recommendations 18 and 19 have

							It appears that azithromycin IV has not been considered as a macrolide choice; please see point 4 for further discussion.	been removed.
62	SH	Aspire	6	FULL	10.8.4 Table 100	263	In this section the following statement is written: *'For the macrolide component, the GDG felt that naming clarithromycin as an example was justified based on side-effect profile and cost'* Please see point 3 and point 4 for a discussion of the side effect profile. Please see point 1 for the cost azithromycin IV. Based on appendix O of the full guidelines, the cost of Klaricid IV is £18.90/day whereas Zedbac 500mg powder for solution for infusion costs £9.50/ day.	Thank you for your comments. The developers have amended the wording of the table (now Table 101) and the associated recommendations which now does not include any examples. The GDG recommended macrolides as an antibiotic group to form one component of empirical dual therapy. This recommendation was made by GDG consensus as little high quality direct evidence was available, and most of the dual therapy regimes in the cohort studies did not include azithromycin. The GDG has not made any specific recommendation against azithromycin, leaving the potential for its use as the macrolide component in dual therapy open. The cost of Zedbac has been added to Appendix O and clinicians are expected to refer to SmPCs when making prescribing decisions about formulation.
37	SH	Royal College of Pathologists	1	FULL	10.8.40	264	In the last paragraph on this page reference is made to "numerous alternative antibiotic regimes that would be reasonable for use in patients with high severity CAP who are unable to receive a component of empirical antibiotic therapy (for example due to allergy)". Is the GDG able to give examples of such regimes in particular in the context of penicillin/beta lactam allergy and also provide examples of "number of factors requiring consideration"?	Thank you for your comment. The GDG felt able to recommend alternative antibiotic therapy for patients with beta-lactam allergy because there was evidence that a tetracycline or macrolide are effective for low-severity CAP. However, for moderate- to high-severity CAP, the evidence was less convincing and the GDG refrained from making a specific recommendation. In this circumstance current practice is

								presumed to be upheld and it is expected that local policies for patients with allergy would be followed. The linking evidence to recommendations table (Table 101, page 265) has been expanded to suggest that clinicians should liaise with local microbiology services to ensure adequate empirical cover for common pathogens for patients with moderate-severity community-acquired pneumonia who are allergic to penicillin when an alternative is not clear.
59	SH	Aspire	3	FULL	10.9.4 Table 105 row 7 column 2	P275	In this section the following statement is written: '*Heightened concerns regarding cardiovascular, ototoxic and hepatotoxic effects of azithromycin in comparison to clarithromycin were also felt to outweigh the potential benefits of a shorter antibiotic duration and ease of administration with once-daily dosing'* We will address each of these heightened concerns individually as we feel that this statement could warrant further review. *Cardiovascular* Azithromycin was shown to have an increased risk of cardiovascular death compared with amoxicillin or ciprofloxacin, but was not shown to differ from levofloxacin. (Ray et al, 2012) In a recent study, an increased risk of death or serious arrhythmia compared with amoxicillin in days 1-5, but not in days 1-10 was shown. (Rao et al, 2014) However these papers do not compare the relative risks within the macrolide class. In addition to these studies, azithromycin was shown to have no increased risk of death from cardiovascular causes in a general population of young and middle-aged	Thank you for your comments. The GDG acknowledges the points you reference. The developers have removed the sentence from the guideline and have changed the relevant recommendation, omitting specific examples.

							adults. (Svanstrom et al, 2013) In older patients, use of azithromycin compared with other antibiotics (these included respiratory fluoroquinolone with or without an appropriate Beta-lactam) showed a lower risk of 90-day mortality and a smaller increased risk of myocardial infarction, which is consistent with a net benefit associated with azithromycin use. (Mortensen et al, 2014) The incidence of spontaneous reports for Torsades de Pointes against the number of prescriptions from 1993-2000 in America was 0.06 cases per million for azithromycin and 0.18 cases per million for clarithromycin. (Altenburg et al, 2011) In a non-clinical study in rats, investigating the risk of QT-prolongation caused by macrolides, the rank order of risk (from highest to lowest) was: erythromycin > clarithromycin > roxithromycin and azithromycin. (Ohtani et al, 2000) Clinically, azithromycin has been shown to be the safest of the macrolides in terms of cardiac toxicity. (Guo et al, 2010) (Owens and Nolin, 2006) (Mortensen et al, 2014) PRAC (pharmacovigilance risk assessment committee) safety signals have been detected for clarithromycin and azithromycin for long-term ischaemic effects and for cardiac arrhythmia respectively. The conclusion from PRAC with regards to ischaemic effects in clarithromycin was that there was not enough clinical evidence to draw a conclusion and that there should be further exploration of clinical data in the next PSUR (periodic safety update report). (PRAC meeting minutes, 2013) The current conclusion from PRAC for azithromycin is that there is not enough evidence to support a change in the SmPC for azithromycin and that further assessment is required. (PRAC meeting minutes, 2013-14) The	

							SmPC for azithromycin currently states that there is a possibility of QTc prolongation due to a class effect. Whereas the SmPC for clarithromycin has a much stronger warning for QTc prolongation reflecting the increased potential for cardiac toxicity of clarithromycin compared with azithromycin. *Ototoxicity* Ototoxicity (reversible hearing loss or deafness) is stated as a common side effect on the SmPC for Zedbac and as a very rare and not known side effect for Klaricid IV and this is reflected in the literature showing reversible hearing loss from administration of 500mg azithromycin/ day. (Altenburg et al, 2011)The problem of ototoxicity is well documented across antimicrobials in general and has also been reported in clarithromycin. (Schellack et al, 2012) *Hepatotoxicity* Although hepatotoxicity is a problem associated with azithromycin, it has also been reported in clarithromycin and is strongly associated with antimicrobials in general. (Stine & Lewis, 2013). In the SmPCs for both clarithromycin IV and azithromycin IV, hepatotoxicity is listed as a side effect with the same frequency and has the same warning. Please also see point 4 for a discussion of the further benefits of the use of azithromycin compared with clarithromycin.	
16	SH	British Geriatric Society	4	FULL	14.1		Discharge: We would agree with the criteria proposed for a safe discharge, but would as above advocate early and rapid multidisciplinary assessment of older adults and early mobilisation to avoid deconditioning. We appreciate there is some reference to patients'	Thank you for your comment. We looked for evidence specific to older populations. We found very little, but it is important to emphasise that the average age of the subjects in most of the studies

							"social circumstances" and "quality of life" but it is really important that "comprehensive geriatric assessment" (CGA) is undertaken on respiratory and all general wards in patients over 75 with multiple morbidities or frailty as this process lowers overall mortality rates, and is inadequately taken up in UK general hospitals. This includes, for example, a holistic multidisciplinary assessment of physical and cognitive function, medication review, social circumstances, risk of falls and other comorbidities. Many references are available to support this statement but this BGS review summarises the evidence: http://www.bgs.org.uk/index.php?option=com_content&view=article&id=1669:cgsellisreview&catid=87:interfacegeriatrics&Itemid=146 We are happy to provide more information on the approach to frailty and CGA if the GDG decides to pick up this theme.	was high, because pneumonia is much commoner in older people. In other words, all our Recommendations very much reflect best management of pneumonia in older people. There was a care of the elderly physician on the Group (indeed there were 2 for some of the time) who contributed fully to deriving the recommendations. For the discharge review question, the GDG considered studies which included older people when available. The studies included in the severity assessment review used all patients presenting, including older people and those with comorbidities. The recommendations in this guidance are therefore relevant to this population. We have added detail about frail elderly patients to the linking evidence to recommendations safe discharge section (Table 140, page 350). An analysis of and recommendations for comprehensive assessment of the older person is outside the scope for this guidance.
1	SH	Association of Chartered Physiotherapists in Respiratory Care (ACRPC).	1	NICE	General	General	Our comments are as follows… consider adding the following statement into the document 'if patients are having difficulty with sputum clearance as a result of their infection a referral to physiotherapy is recommended"	Thank you for your comment. Physiotherapy and specific management of sputum clearance were not identified for systematic review (see section 4.3.2d) of the scope) and the GDG are therefore unable to make any recommendations on these topics.
12	SH	Royal College	2	NICE	General	General	Our reviewers particularly valued the abbreviated	Thank you for your comment.

		of Physicians of Edinburgh.					version which is concise, clear and presents all relevant information. Professor Woodhead and his team are to be congratulated on this guideline.	
43	Alere	Alere	2	NICE	1.1.1	9	We very much welcome the recommendation to consider a C-reactive protein POCT for patients presenting in primary care, if it is not clear from clinical assessment whether antibiotics should be prescribed. We would, however, like to suggest to the Guideline Development Group that the recommendation for C-reactive protein POCT in primary care could perhaps be stronger, particularly in the light of recent new evidence and its widespread use in other European countries. C-reactive protein POCT is already used routinely in primary care in a number of other countries (including Denmark, Norway, Sweden, Germany, The Netherlands, Switzerland and Finland) where it has helped reduce the rates of antibiotic prescribing by as much as 15-20% (Little P *et al*. 2013; Hopstaken RM *et al*. 2003; Cals JWL *et al*. 2010b; Jakobsen KA. 2010; Diederichsen HZ *et al*. 2000; Bjerrum L *et al*. 2005). By using the C-reactive protein test as an aid to help primary care practitioners better identify which patients require antibiotics, and to differentiate from those who do not, this recommendation has the potential to optimise prescribing practice, promoting rational prescribing of antibiotics in accordance with the Department of Health's Antimicrobial Resistance Strategy and, ultimately, improving patient safety. We believe this is particularly important, given that: (i) According to section 1.1.1, following the clinical assessment, the result of the C-	Thank you for your comments. The GDG feels that the strength of the recommendation reflects the level of evidence reviewed in this guideline.

							reactive protein test is then needed in order to guide the antibiotic prescribing decision; and (ii) 80% of antibiotic prescribing takes place in primary care (Royal College of General Practitioners, Public Health England and the Antimicrobial Stewardship in Primary Care (ASPIC). TARGET Antibiotic toolkit. http://www.rcgp.org.uk/clinical-and-research/target-antibiotics-toolkit.aspx International comparisons confirm that antibiotic resistance rates are strongly related to antibiotic use in primary care. The overall antibiotic prescribing rate in the UK is still significantly higher than in those countries where C-reactive protein POCT is used and where the level of antibiotic resistance is consequently lower (European Centre for Disease Prevention and Control: Surveillance of antimicrobial consumption in Europe 2011).	
44	Alere	Alere	3	NICE	1.1.1	9	In our opinion, it would be helpful if the term "clinical assessment" was defined, to clarify what "clinical assessment" means in the context of this recommendation and precisely how the use of a C-reactive protein test can help aid primary care decision-making. There are several professional guidelines that are relevant here: The European Respiratory Society guidelines, the British Thoracic Society guidelines, the Scottish Intercollegiate Guidelines Network guideline 59 on the Community Management of Lower Respiratory Tract Infection in Adults and NICE clinical guideline 69.	Thank you for your comment. Since there is no accepted definition of clinical assessment and because the GDG did not examine studies' use of clinical assessment, the GDG does not consider it possible to discuss this further.
45	Alere	Alere	4	NICE	1.1.3	10	Again, we believe it would be helpful to practitioners to clarify what "clinical judgement" means in the context of this recommendation.	Thank you for your comment. Since there is no accepted definition of clinical judgement and because the GDG did not examine studies' use of clinical

								assessment, the GDG does not consider it possible to discuss this further.
42	SH	Alere	1	NICE	1.1.1 – 1.1.22	9-14	Alere Limited ("we") thank the Guideline Development Group for the opportunity to comment on this draft guideline. As a general comment, we found the long list of different diagnostic, assessment, management and treatment options detailed in recommendations 1.1.1 – 1.1.22 very difficult to follow. In particular, the statement "… if it is not clear after clinical assessment whether antibiotics should be prescribed..." is rather unclear. We feel that the final guideline would benefit from the inclusion of a statement of the evidence-based aspects for "clinical assessment" and a simple algorithm of the recommendations as a patient pathway. This algorithm could include an evidence-based definition of "clinical assessment", the C-reactive protein test and prescribing indicators (1.1.1) and a CRB-65 risk score calculator to facilitate integration with the primary care EMIS system. Specific algorithms have already been developed (for example, in The Netherlands) where C-reactive protein point of care test (POCT) thresholds help guide decision-making for antibiotic prescribing (if <20 mg/l, antibiotics would not be prescribed in the absence of other clinical contra-indications). A copy of the Dutch algorithm is included in the Dutch General Practice guidelines (Verheij ThJM *et al*. 2011).	Thank you for your comment. The GDG is not advocating delayed prescription for patients with a clear clinical diagnosis of pneumonia, or with CXR-confirmed pneumonia. The GDG has changed the • wording of the CRP recommendation to highlight that the recommendation is only applicable in instances in which a diagnosis of pneumonia has not been made, and • heading to the CRP recommendation ("Presentation with symptoms of lower respiratory tract infection") in order to further emphasize that only patients with symptoms which raise the possibility of pneumonia but in whom there is uncertainty about the need for antibiotics are considered for CRP testing (i.e. those with clinically suspected pneumonia should receive antibiotics as soon as possible, and those thought clinically to have a self-limiting RTI should receive no antibiotic therapy). • the subheadings in the full list of recommendations to clarify specific management aspects of LRTI, CAP (low-, moderate- and high-severity) and HAP. The GDG also considered its use as a point of care test within the community.

								Detailed explanations about the necessary considerations in order to maximise outcomes have been included in the evidence and link to recommendations in Table 16, section 7.5, page 77. The CRP recommendation now allows a more sophisticated approach to risk stratification in people with clinically undetected pneumonia than is currently possible. Finally, the GDG note that NICE Guideline CG69 (LRTI) currently recommends a delayed antibiotic prescription.

These organisations were approached but did not respond:

ADDEPT
Aintree University Hospital NHS Foundation Trust
Alder Hey Children's NHS Foundation Trust
Allocate Software PLC
Alzheimer's Society
Association of Ambulance Chief Executives
Association of Anaesthetists of Great Britain and Ireland
Association of Respiratory Nurse Specialists
Basilea Pharmaceutica International Ltd
Betsi Cadwaladr University Health Board
Black and Ethnic Minority Diabetes Association
Boehringer Ingelheim
Brahms UK Limited-Thermo Fisher Scientific
British Liver Trust
British Medical Association
British Medical Journal

British National Formulary
British Nuclear Cardiology Society
British Pharmacological Society
British Psychological Society
British Red Cross
British Society for Allergy & Clinical Immunology
British Society for Antimicrobial Chemotherapy
British Society for Disability and Oral Health
Calderdale and Huddersfield NHS Trust
Cambridge University Hospitals NHS Foundation Trust
Capsulation PPS
Care Quality Commission
Central London Community Health Care NHS Trust
Chartered Society of Physiotherapy
Clarity Informatics Ltd
Clinigen Healthcare
Covidien Ltd.
Croydon Clinical Commissioning Group
Croydon Health Services NHS Trust
Croydon University Hospital
Cumbria Partnership NHS Trust
Department of Health, Social Services and Public Safety - Northern Ireland
Diabetes UK
East and North Hertfordshire NHS Trust
East Kent Hospitals University NHS Foundation Trust
Ethical Medicines Industry Group
Faculty of Intensive Care Medicine
Five Boroughs Partnership NHS Trust
GP update / Red Whale
Greater Manchester & Beyond Coalition of PLW & HIV
Group B Strep Support
Health & Social Care Information Centre
Health and Care Professions Council
Health Protection Agency
Healthcare Improvement Scotland
Healthcare Infection Society
Healthcare Quality Improvement Partnership
Healthwatch East Sussex

Herts Valleys Clinical Commissioning Group
Hindu Council UK
Hockley Medical Practice
Humber NHS Foundation Trust
ICU Steps
Independent Healthcare Advisory Services
Institute of Biomedical Science
Joint Royal Colleges Ambulance Liaison Committee
Lancashire Care NHS Foundation Trust
Launch Diagnostics
Leeds Community Healthcare NHS Trust
Leeds North Clinical Commisioning Group
Leeds South and East Clinical Commissioning Group
Local Government Association
London Respiratory Team
Luton and Dunstable Hospital NHS Trust
Maquet UK Ltd
Medicines and Healthcare products Regulatory Agency
Mid Cheshire Hospitals NHS Trust
Ministry of Defence (MOD)
MRSA Action UK
National Association of Primary Care
National Clinical Guideline Centre
National Collaborating Centre for Cancer
National Collaborating Centre for Mental Health
National Collaborating Centre for Women's and Children's Health
National Deaf Children's Society
National Institute for Health Research Health Technology Assessment Programme
National Institute for Health Research
National Kidney Federation
National Patient Safety Agency
Newcastle upon Tyne Hospitals NHS Foundation Trust
NHS Barnsley Clinical Commissioning Group
NHS Choices
NHS Connecting for Health
NHS County Durham and Darlington
NHS Cumbria Clinical Commissioning Group
NHS Hardwick CCG

NHS Health at Work
NHS Improvement
NHS Leeds West CCG
NHS Luton CCG
NHS Medway Clinical Commissioning Group
NHS North Somerset CCG
NHS Plus
NHS Sheffield
NHS South Cheshire CCG
NHS Wakefield CCG
NHS Warwickshire North CCG
NHS West Hampshire CCG
North Essex Partnership Foundation Trust
North of England Commissioning Support
North of England Critical Care Network
North West London Hospitals NHS Trust
Nottingham City Council
Nursing and Midwifery Council
Oxford Health NHS Foundation Trust
Oxfordshire Clinical Commissioning Group
Pan London Acute Medicine Network
Pathfinders Specialist and Complex Care
Pfizer
PHE Alcohol and Drugs, Health & Wellbeing Directorate
PrescQIPP NHS Programme
Primary Care Pharmacists Association
Primary Care Respiratory Society UK
Primrose Bank Medical Centre
Public Health Agency for Northern Ireland
Public Health England
Public Health Wales NHS Trust
Public Health Wales NHS Trust
Queen Elizabeth Hospital King's Lynn NHS Trust
Robert Jones & Agnes Hunt Orthopaedic & District Hospital NHS Trust
Royal Brompton Hospital & Harefield NHS Trust
Royal College of Anaesthetists
Royal College of General Practitioners
Royal College of General Practitioners in Wales

Royal College of Midwives
Royal College of Obstetricians and Gynaecologists
Royal College of Paediatrics and Child Health
Royal College of Physicians
Royal College of Physicians and Surgeons of Glasgow
Royal College of Psychiatrists
Royal College of Surgeons of England
Royal Cornwall Hospitals NHS Trust
Royal Pharmaceutical Society
Royal Society of Medicine
Salisbury NHS Foundation Trust
Scottish Clinical Virology Consultants Group
Scottish Intercollegiate Guidelines Network
Sheffield Children's Hospital
Sheffield Teaching Hospitals NHS Foundation Trust
Skills for Care
Social Care Institute for Excellence
Society and College of Radiographers
Society for General Microbiology
South London & Maudsley NHS Trust
South Wales Critical Care Network
South West Yorkshire Partnership NHS Foundation Trust
Southport and Ormskirk Hospital NHS Trust
Spectranetics Corporation
St John Ambulance
St Mary's Hospital
Staffordshire and Stoke on Trent Partnership NHS Trust
Stockport Clinical Commissioning Group
Taunton & Somerset NHS Foundation Trust
Terrence Higgins Trust
Thames Reach
The Association for Clinical Biochemistry & Laboratory Medicine
The Lullaby Trust
The Orders of St John Care Trust
The Patients Association
The Stroke Association
Torbay and Southern Devon Health and Care NHS Trus
United Kingdom Sepsis Group

University Hospital Birmingham NHS Foundation Trust
University Hospital of North Staffordshire NHS Trust
University Hospitals Birmingham
Walsall Local Involvement Network
Welsh Ambulance Services NHS Trust
Welsh Government
Welsh Scientific Advisory Committee
Western Sussex Hospitals NHS Trust
Westminster Local Involvement Network
Wigan Borough Clinical Commissioning Group
York Hospitals NHS Foundation Trust