Managing Common Infections

Pneumonia (community-acquired): antimicrobial prescribing

Stakeholder comments table

12/02/2019 – 11/03/2019

ID	Organisation	Document	Page No.	Line No.	Comments	Developers Response
1	Royal College of Paediatrics and Child Health and Neonatal and Paediatric Pharmacists Group (joint medicines committee)	Pneumonia (community-acquired): antimicrobial prescribing Full version	6-7	Table 2	There is limited information on which antibiotics to use and amoxicillin for non-severe seems reasonable and in line with BTS guidance. Issue around treatment for severe. Limited evidence on the choice suggested for severe, based on one small study used in a different population. Should it not slightly depend on local microbiology populations? In those with severe, would it not be worth including an atypical cover as standard?	Thank you for your comment. The committee was aware that there was limited evidence available for children with severe community-acquired pneumonia and therefore based the recommendations on its experience of which antibiotic would be most likely to target the causative pathogens and provide broad spectrum antimicrobial cover. Recommendation 1.1.1 states that local antimicrobial resistance and surveillance data should be considered when choosing an antibiotic. The committee discussed that atypical cover is not required routinely in children, as infection with atypical pathogens is uncommon and it is easier to diagnose than in adults.
2	Royal College of Paediatrics and Child Health and Neonatal and Paediatric Pharmacists Group (joint	Pneumonia (community-acquired): antimicrobial prescribing Full version	6-7	Table 2: Antibiotics for children and young people under	Regarding the 3 choices of alternative antibiotics given for non-severe symptoms or signs of community acquired pneumonia (CAP): Apart from clarithromycin, there are no other oral antibiotic alternatives suggested for children younger than 8 years of age (to 3 months old). Between the ages of 8 years to	Thank you for your comment. The committee discussed that there was only 1 choice of alternative antibiotic in children under 8 with non-severe community-acquired pneumonia. They agreed that clarithromycin will be suitable for most children and therefore further options are not specified in the prescribing table. It is expected that clinical judgement or consultation with a local

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	medicines committee)	22- 23		18 years;	12 years there is an additional alternative (erythromycin) cited. There is no clear advice as to what to do if the alternative (clarithromycin) cannot be used in children younger than 8 years considering this is the only alternative antibiotic recommended in this guideline for these younger children for non-severe symptoms and signs of CAP	microbiologist would be appropriate for the small number of children in whom amoxicillin or clarithromycin would not be suitable.
3	Royal College of Paediatrics and Child Health and Neonatal and Paediatric Pharmacists Group (joint medicines committee)	Pneumonia (community-acquired): antimicrobial prescribing Full version	22-23		It is acknowledged that there is limited evidence relevant to UK practice for alternatives to treatment. However, no discussion is provided in the guideline to justify the limited alternatives in children between 3 months to 8 years old compared to older children.	Thank you for your comment. It is expected that clinical judgement or consultation with a local microbiologist would be appropriate for the small number of children with non-severe community-acquired pneumonia in whom amoxicillin or clarithromycin would not be suitable. The committee discussion section has been updated to reflect this.
4	Royal College of Paediatrics and Child Health and Neonatal and Paediatric Pharmacists Group (joint medicines committee)	Pneumonia (community-acquired): antimicrobial Pneumonia (community-acquired): antimicrobial prescribing Full version	22-23		In those with severe staph infection suspected should there be an increase length on treatment to 14 days and addition of other treatment. What is the guidance for complicated severe pneumonias? This does not seem to be included in the guidance	Thank you for your comment. The committee discussed treatment length for people infected with uncommon pathogens including *Staphylococcus aureus* and agreed that certain people may require treatment for longer than 5 days. It agreed that antibiotics should be stopped after 5 days unless microbiology results suggest a longer course length is needed or the person is not clinically stable and amended the footnote in table 1 to state this. The committee discussed that this guideline covers common infections and therefore complicated severe pneumonia is outside the remit of this guideline.

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5	Royal College of Paediatrics and Child Health and Neonatal and Paediatric Pharmacists Group (joint medicines committee)	Pneumonia (community-acquired): antimicrobial prescribing Full	General		NICE have reviewed the evidence, but the current NICE document 'Summary of antimicrobial prescribing guidance – managing common infections' https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/antimicrobial%20guidance/summary-antimicrobial-prescribing-guidance.pdf does use 7 -10 day antibiotic duration for severe CAP. Presumably NICE will also update this document in line with the guideline.	Thank you for your comment. The NICE/PHE summary of antimicrobial prescribing guidance will be updated to reflect the recommendations made in this antimicrobial prescribing guideline.
6	The British Society for Antimicrobial Chemotherapy	Guideline	5		Severe CAP suggests oral or IV. The foot note says give oral if the person can take oral and the severity does not require IV antibiotics. I think there needs to be some indication here about what would prevent the use of oral antibiotics. If the patient was not absorbing from the gut then that would warrant IVs but what else would? The BTS guideline says severe CAP should receive IV antibiotics. Currently in my hospital nearly all CAP patients receive IV antibiotics so advocating orals for all severity will be a bit change in practice (one I applaud) but some insight in to who we'd expect to give IV antibiotics to would be useful	Thank you for your comment. The committee was not able to specify which people with high-severity community-acquired pneumonia may require intravenous antibiotics based on the available evidence and agreed that this decision would need to be based on clinical judgement. Therefore, no changes have been made to the current footnote on giving intravenous antibiotics.
7	The British Society for Antimicrobial Chemotherapy	Guideline	5	6	Question 4: We are concerned about the total treatment duration of 5 days for all severities of pneumonia and the quality and applicability of the evidence that this is based upon (given that the clinical definition of 'severity' can vary and if mortality is used, the majority of studies have mortality <3% and hence describe low severity presentations).	Thank you for your comment. The committee discussed treatment length for people with community-acquired pneumonia of all severities and those infected with uncommon pathogens including *Staphylococcus aureus* and *Legionella pneumophila.* The committee agreed that certain people may require treatment for longer than 5 days. It agreed that antibiotics should be stopped after 5 days

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					Locally, we advise clinical review at day 3, with antibiotic stop if alternative diagnosis confirmed, individualisation of therapy according to patient response with standard course length of 5 days for low severity CAP, 7 days for moderate severity CAP and 7-10 days for high severity CAP (extending to 10-14 days for Legionella, S. aureus and Gram negative pneumonia).	unless microbiology results suggest a longer course length is necessary or the person is not clinically stable and amended the footnote in table 1 to state this. This guideline does not cover diagnosis and provides recommendations for people with a confirmed diagnosis of community-acquired pneumonia. Therefore, it is outside the scope of this guideline to make recommendations on stopping antibiotics based on alternative diagnosis.
8	The British Society for Antimicrobial Chemotherapy	Guideline	5	6	Question 4: We are concerned about the additional of atypical cover with a macrolide being left to the discretion of the prescriber for non-severe CAP given the clinical complexity/challenge of determining whether infection is caused by Mycoplasma, Chlamydia or Legionella in the absence of rapid and accurate diagnostics.	Thank you for your comment. The committee discussed the difficulties in diagnosing infection with an atypical pathogen. However, it agreed that in people with moderate-severity community-acquired pneumonia, the risk of harm of undertreatment if dual therapy is not offered is low. Clinical judgement should be used to determine if atypical infection is likely, in which case it is appropriate to have an option to provide dual therapy. The committee agreed that the risk of harm from overtreatment in people who do not have an atypical infection is mitigated by the recommendation to review microbiological test results when available and to change the antibiotic using a narrower spectrum antibiotic, if appropriate. The committee discussed that atypical pathogens such as *Mycoplasma pneumoniae* occur in outbreaks, on average, every 4 years. A footnote has been added to state this to provide further guidance for when to provide atypical cover.
9	The British Society for	Guideline	6		Footnote number 4 “stepping down to oral if possible” change to “stepping down to oral if	Thank you for your comment. The committee discussed the wording of this footnote.

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	Antimicrobial Chemotherapy				patient responding appropriately". I think most people will know what if possible means but some clarity may be useful.	However, there are multiple reasons that switching to oral antibiotics might not be possible, for example not being able to tolerate oral medicines. Therefore, the committee agreed that the footnote should remain unchanged but agreed to change the term 'stepping down to' to 'switching to'.
10	The British Society for Antimicrobial Chemotherapy	Guideline	6		Footnote 5. This is a big change in practice. Would it be worth putting the IDSA and Uranga study criteria for stopping at day 5 in here to give clinicians confidence to stop at day 5. E.g. systolic less than 90mmHg, HR less than 100 etc. I can see the merit of not defining these but I think given that this is such a change in practice more specific advice may help clinicians.	Thank you for your comment. The footnote has been updated to include the specific criteria used in the Uranga et al. (2016) study for reviewing antibiotics after the first 5 days of treatment.
11	The British Society for Antimicrobial Chemotherapy	Guideline	6		'Consider adding a macrolide to amoxicillin if atypical pneumonia suspected. Review when susceptibilities available and stop the macrolide if atypical bacteria are not isolated.'	Thank you for your comment. This footnote has been amended based on this and other stakeholder comments.
12	The British Society for Antimicrobial Chemotherapy	Guideline	10	14	Looks like Aliberti study does not support the physician guided approach to stopping antibiotics?	Thank you for your comment. Aliberti et al. 2017 found that there is no difference between physician-guided stopping of antibiotics compared with stopping antibiotics after 5 days if the person has been clinically stable for 48 hours. For more information please see the section on antimicrobial prescribing strategies in a mixed severity population in the evidence review.
13	The British Society for Antimicrobial Chemotherapy	Guideline	21		"The committee noted that adults with high-severity community-acquired pneumonia will be managed in a high-dependency or an intensive care unit, and are easily	Thank you for your comment. This statement has been removed from the guideline.

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					distinguishable from adults with moderate-severity community-acquired pneumonia". This is not strictly true, many CURB65 >3 patients (many elderly patients) are not managed in HDU/ITU but on the general wards.	
14	The British Society for Antimicrobial Chemotherapy	Guideline	21		"The macrolide can be stopped if an atypical infection is not isolated" our hospital lab doesn't not look for atypical organisms except legionella antigens in urine. I don't think we are alone with that as such I am not sure if this sentence is applicable to many organisations?	Thank you for your comment. The recommendations for microbiological testing cross-refer to the recommendations in the NICE guideline on pneumonia (CG191). This recommends: "For people with moderate- or high-severity community-acquired pneumonia: • take blood and sputum cultures and • consider pneumococcal and legionella urinary antigen tests." However, the committee discussed the difficulties in diagnosing atypical infection and therefore agreed that the decision to stop the macrolide should be reviewed based on microbiological results instead of necessarily stepping down if atypical pathogens are not isolated. Therefore, clinical judgement can be used alongside the available microbiological test results to determine if stepping down from dual therapy is appropriate.
15	The British Society for Antimicrobial Chemotherapy	Guideline	21		"Based on their experience, the first choice antibiotic for adults with high-severity community-acquired pneumonia is co-amoxiclav" I am not sure how this conclusion is reached given the evidence cited above. The evidence above suggests that penicillin + macrolide is as effective as levofloxacin.	Thank you for your comment. The committee discussed the evidence for moderate- to high-severity community-acquired pneumonia and agreed that levofloxacin should not be recommended first-line due to the MHRA safety advice. The discussion section describes that the committee recognised that

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					There isn't any evidence above that demonstrates superiority of beta-lactam / beta-lactamase inhibitor + macrolide over other regimens. There is an emerging argument that we need to cover Gram negatives enteric bacteria and also that haemophilus influenzae resistance rates to amoxiclav mean use need to use a beta-lactamase inhibitor. Is that the reason for the decision here? As it stands the rationale doesn't follow the evidence listed	there is not clear evidence that the addition of a macrolide to amoxicillin is effective for treating moderate- to high-severity community acquired pneumonia, however it had concerns about the consistency and quality of the evidence. Therefore, the recommendations for high-severity community-acquired pneumonia are based on the committee's experience. The committee agreed that in people with high-severity community-acquired pneumonia, the high risk of death outweighed the potential adverse effects and increased risk of antimicrobial resistance. Therefore, co-amoxiclav with a macrolide is the first-line choice for this population, as this provides broad-spectrum gram negative cover and covers atypical pathogens.
16	The British Society for Antimicrobial Chemotherapy	Guideline	General		Don't see a change to the BTS guidelines.	Thank you for your comment. The guideline has been developed in accordance with the processes and methods set out in the interim process guide for antimicrobial prescribing guidelines, which is a different process to the BTS guideline. There may be differences in the evidence considered and the recommendations made.
17	The British Society for Antimicrobial Chemotherapy	Guideline	General		Cotrimoxazole should be considered as an agent for CAP where doxycycline is not suitable empirical option due to allergy or intolerance as most community isolates remain susceptible. The same is not true for macrolides.	Thank you for your comment. The committee discussed co-trimoxazole as an alternative option in low-severity community-acquired pneumonia. However, the committee agreed there are concerns about the adverse events associated with co-trimoxazole, and in the absence of evidence identified for co-trimoxazole in adults, there was insufficient evidence to recommend this.

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18	British Paediatric Allergy, Immunology & Infection Group	Draft guideline	3	12	It should be made clearer that microbiological investigations for children are of very limited value and should only be used for severely ill children in hospital. Sputum samples have very low yield and high contamination rate. Nasopharyngeal swabs/aspirates for viruses may be useful in children to help distinguishing from bacterial infection. Urine pneumococcal could be a useful non-invasive investigation in older children. The guideline gives no reference for this recommendation. A useful review is cited here: Clark J, Arch Dis Child 2015; 100: 193-97	Thank you for your comment. The committee discussed the use of microbiological tests in children and agreed that these should not be limited to respiratory tests. The committee also agreed that these tests should be limited to children with severe symptoms or signs, or with a comorbidity. The recommendation on microbiological testing in children has been updated to reflect these decisions. Regarding the highlighted reference (Clark, 2015): this article will not be included in the evidence review as it does not meet the review protocol criteria as it is a narrative review.
19	British Paediatric Allergy, Immunology & Infection Group	Draft guideline	7	Table	Choice of co-amoxiclav for severe infection: Not severity should determine use of antibiotics but expected pathogen. Severe infection may still respond well to amoxicillin. Clinical factors, such as mechanism of infection (e.g. aspiration pneumonia? underlying lung condition? expected higher resistance organisms?) should determine choice rather than severity. From an antimicrobial stewardship perspective, cefuroxime would be a better choice for iv treatment because of the reduced anaerobe coverage in particular over co-amoxiclav. From an antimicrobial stewardship perspective there are significant concerns about more widespread use of co-amoxiclav (ESBL, c. diff). From my own experience working in Singapore, where co-amoxiclav use is more widespread, I can report that genuine c. diff infection in children has	Thank you for your comment. The committee discussed the recommendation for first-line antibiotic choice in children with severe community-acquired pneumonia and agreed that co-amoxiclav covers the most common causative organisms. The rationale for recommending co-amoxiclav over amoxicillin in this population is that the risk of harm from undertreatment is greater than in children with non-severe community-acquired pneumonia and that the risk of adverse effects and increased antimicrobial resistance is likely to be outweighed by the clinical benefit. Recommendation 1.1.1 states that the risk of developing complications (for example if the person has a relevant comorbidity), recent antibiotic use and recent microbiological results including colonisation with multi-drug resistant bacteria, should be taken account of when choosing an antibiotic.

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					become a significant problem. In my view, GP's should be discouraged from using co-amoxiclav for this diagnosis in primary care, and should rather seek a paediatric opinion if they consider prescribing it.	The committee discussed that clinical practice in Singapore is unlikely to be applicable to the UK. Based on its experience, and as no evidence was identified on intravenous cefuroxime in children with severe community-acquired pneumonia, the committee agreed that co-amoxiclav was the most appropriate first choice antibiotic for this population.
20	Scottish Antimicrobial Prescribing Group	Visual summary and guideline	General		We agree with the principles of management and promotion of IVOST/IV review and are very pleased to see the recommendation for 5 days treatment for all emphasised. Key learning point is the 5 day course for pneumonia – this needs to be cascaded down to patients (who have had it stressed repeatedly to 'finish the course') and prescribers, along with the advice that symptoms, especially cough, may persist beyond the 5 days. Key practical implication is at pharmaceutical level to start changing standard packs to 5 days rather than 7 days as currently.	Thank you for your comment. The committee agreed that people with community-acquired pneumonia should be given advice on how long their symptoms are likely to last and noted the recommendations in the NICE guideline on pneumonia (CG191) describing which information should be given. This has been included in the recommendation on advice to be given to people with community-acquired pneumonia. The committee recognised the issue with pack sizes, however agreed that a 5-day course length is still appropriate.
21	Scottish Antimicrobial Prescribing Group	Visual summary and guideline	General		Very little mention is made specifically about Clostridium difficile infection (CDI). Also no reference to adverse events due to clarithromycin which in Scotland has led to removal/reduction of macrolides from local guidance. Choice of antibiotic In CURB 65 0 or 1, we suggest doxycycline should be positioned above macrolides in the	Thank you for your comment. The committee considered the risks of *Clostridium difficile* infection alongside the risk of harm from not adequately treating the infection. The committee discussion section has been updated to reflect this discussion. The committee discussed that macrolides are an appropriate antibiotic class to provide cover for atypical pathogens in this

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					table on basis of lower R rates in S. pneumoniae (both locally in Scotland as well as from across UK as evidenced in BSAC resistance surveillance project). Doxycycline also has H. influenzae cover. In CURB 65 2, little evidence for dual therapy. Could doxycycline be included here? Would it make more sense to list all three and indicate which include atypical cover. CURB65 >=3 – we believe this is where there is some limited evidence for empirical dual therapy. It is difficult to stratify between Amoxicillin and Co-amoxiclav in the guideline and so we understand why the authors have chosen Co-amoxiclav as a default. However we think this is unnecessarily broad for many patients (particularly the elderly who by definition have higher CURB65 scores) and so it would be reasonable to make an allowance for the option of Amoxicillin + Macrolide in selected (elderly) patients based on C. diff risk and established practice/experience in many Scottish health boards.	population, given that fluroquinolones are associated with MHRA safety warnings. The committee discussed the adverse effects which might be associated with macrolide use but agreed that this is outweighed by the risk of harm from undertreatment. The committee agreed that doxycycline should be listed above macrolides for alternative oral antibiotic choices for people with low-severity community-acquired pneumonia. The committee also agreed that doxycycline is a reasonable alternative antibiotic choice for people with moderate-severity community-acquired pneumonia. However, the committee agreed not to include doxycycline as a first choice antibiotic for this population as there is very limited evidence for doxycycline. The committee discussed that doxycycline is not appropriate for dual therapy with amoxicillin and as there is evidence and clinical experience supporting the use of amoxicillin, this should be the first choice antibiotic for moderate-severity community-acquired pneumonia. The committee discussed the first-choice antibiotic choices for high-severity community-acquired pneumonia and noted that severity should be based on clinical judgement and guided by C(U)RB65 score. The committee agreed that people who are judged by a clinician to have high-severity

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						community-acquired pneumonia require a broad spectrum antibiotic due to the high risk of death in this population. The committee noted that there is no evidence showing amoxicillin is effective in a high-severity population and that the risks associated with undertreatment are outweighed by the risks of adverse effects associated with broad spectrum antibiotics.
22	Royal College of General Practitioners	General	General		The RCGP have developed a 'Treat Antibiotics Responsibly, Guidance, Education, Tools' (TARGET) toolkit for primary care teams, which is of relevance to this guideline. The toolkit can be found here: https://www.rcgp.org.uk/clinical-and-research/resources/toolkits/target-antibiotic-toolkit.aspx The RCGP also has resources on Antimicrobial stewardship, here: https://www.rcgp.org.uk/clinical-and-research/resources/a-to-z-clinical-resources/antimicrobial-stewardship.aspx	Thank you for your comment and for highlighting these resources. We are aware of the TARGET toolkit which includes links to NICE antimicrobial prescribing guidelines and the resources on antimicrobial stewardship.
23	Royal College of General Practitioners	Draft Guideline	4	1.10	The advice about whether to send a sputum sample if possible before prescribing antibiotics in the Community is unclear and should be clarified	Thank you for your comment. The recommendations for microbiological testing in adults with community-acquired pneumonia cross refer to the NICE guideline on pneumonia (CG191), which state: • Do not routinely offer microbiological tests to patients with low-severity community-acquired pneumonia. • For patients with moderate- or high-severity community-acquired pneumonia, take blood and sputum

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						cultures and consider pneumococcal and legionella urinary antigen tests. The recommendation for microbiological testing in children with community-acquired pneumonia has been updated to clarify in which children microbiological tests should be considered (children in hospital with community-acquired pneumonia and severe symptoms or signs or a comorbidity).
24	Royal College of General Practitioners	Draft Guideline	General		The main NICE Community-Acquired Pneumonia Guideline has recommendations on prescribing antibiotics on the basis of C-reactive protein (CPR) testing. This is not mentioned in this Antibiotic Guideline. Since recommendations are being made on the basis of CRB65 the role of CRP should be mentioned.	Thank you for your comment. The diagnosis of community-acquired pneumonia is out of scope for this antimicrobial prescribing guideline. The committee agreed that it was important to use the C(U)RB65 score to guide severity assessment in community-acquired pneumonia which has already been diagnosed, in line with the NICE guideline on pneumonia (CG191). However, the C-reactive protein test is used to diagnose pneumonia in people with symptoms of lower respiratory tract infection. As this relates to diagnosis of pneumonia, C-reactive protein testing is out of scope and therefore will not be included in this antimicrobial prescribing guideline.
25	Royal College of General Practitioners	Quick guide	1		The committee should consider the feasibility of recommending nasopharyngeal swabs for children. These are difficult to do with young children and, as children deteriorate and recover quicker than adults, the benefits may be limited.	Thank you for your comment. The committee discussed the potential difficulties with obtaining nasopharyngeal samples in children and agreed to remove reference to this test.

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26	Royal Pharmaceutical Society	Guideline	5	Table 1	Why is doxycycline excluded from the list of agents that can be used in moderate-severity or high-severity pneumonia? The evidence base quotes a study (Nemeth *et. al.* 2015) showing non-inferiority between levofloxacin and doxycycline and grades this as high quality evidence. Yet levofloxacin is included in the treatment options, but doxycycline is not. This could significantly impact on the many organisations using doxycycline as a second agent in moderate to severe CAP and drive them (if implemented as intended) towards macrolides, with increased adverse drug reactions, costs and potential impact on external national targets of reducing Watch class antibiotics. Is there definitive evidence to suggest that use of doxycycline is inferior to these choices and if not, what was the committee's rationale for excluding the drug at this stage?	Thank you for your comment. The committee agreed that doxycycline is a reasonable alternative antibiotic choice for people with moderate-severity community-acquired pneumonia and have added this as an alternative option for this population. However, the committee agreed not to include doxycycline as a first choice antibiotic for this population as there is very limited evidence for doxycycline. The committee discussed that doxycycline is not appropriate for dual therapy with amoxicillin and as there is evidence and clinical experience supporting the use of amoxicillin, this should be the first choice antibiotic for moderate-severity community-acquired pneumonia. The committee also discussed doxycycline for treatment of high-severity community-acquired pneumonia. However, the committee considered the volume of the evidence for levofloxacin in this population and noted that the evidence for doxycycline came from 1 small study. Therefore, the committee agreed to recommend levofloxacin as an alternative antibiotic for adults with high-severity community-acquired pneumonia.
27	Royal Pharmaceutical Society	Guideline	5	Table 1	We are concerned about the firm recommendation in the table as well as in the text about first-line use of oral antibiotics in severe pneumonia. The text qualifies this with "…and the severity of their condition does not require intravenous antibiotics" footnote 3 in Table 1, but by definition these	Thank you for your comment. The committee discussed the evidence for route of administration which showed that oral antibiotics are more effective than injectable antibiotics for children and young people with severe community-acquired pneumonia. The committee noted that there was no evidence

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					patients are severely unwell with high risk of death and so why has the oral option been so strongly recommended here?	identified on first-line intravenous antibiotics compared with oral antibiotics in adults. However, based on their experience, the principles of antimicrobial stewardship, and supported by the evidence in children, the committee agreed that adults with high-severity community-acquired pneumonia may be able to have oral antibiotics in certain circumstances, but that some people will require intravenous antibiotics and this decision should be based on clinical judgement.
28	Royal Pharmaceutical Society	Guideline	5	Table 1	We are of the opinion that the term “atypical pneumonia” was redundant as per BTS guidelines 2009, yet it’s included here?	Thank you for your comment. The committee agreed to amend the term used to ‘atypical pathogens’.
29	Royal Pharmaceutical Society	Guideline	5	Table 1	Assuming that one of the main user groups for this guidance would be junior doctors on acute medical takes and one of the statements from the 2009 BTS guidelines is that the atypical pathogens “are characterised by being difficult to diagnose early in the illness”, shouldn’t *all* patients have a second agent added to cover for the risk of atypical pathogens, until appropriate testing can rule their presence out? The provided evidence suggests that up-front atypical pathogen coverage is better than adding cover only with a firm diagnosis and as initial suspicion of atypical pathogens will be most likely beyond the skills and experience of most junior doctors, there is a risk that they will *not* suspect it and only give monotherapy, so leading to potential harm.	Thank you for your comment. The committee recognised the difficulties in diagnosing pneumonia caused by atypical pathogens. The committee agreed that people with low- and moderate-severity community-acquired pneumonia are at low risk of harm from not having atypical cover, but that if infection with an atypical pathogen is suspected in these populations, the option to provide atypical cover should be given. The committee discussed the evidence showing that upfront atypical cover is more effective than adding atypical cover after diagnosis of an atypical infection. However, the committee agreed that the increased risk of adverse effects and antimicrobial resistance from using broad spectrum antibiotics upfront was outweighed by the risk of harm in people with low- or moderate-

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						severity community-acquired pneumonia all being offered antibiotics with atypical cover.
30	Royal Pharmaceutical Society	Guideline	6	Table 2	There is increasing evidence that doxycycline can be given in children of all ages for short courses (AAP Red Book 2018, section 4 & J Pedatrics 2015; 166: 1246)	Thank you for your comment. Due to changes in the British National Formulary for Children (BNFc) regarding the age restrictions for doxycycline, the committee agreed to include a footnote linking to the BNFc, for information about the appropriate use of doxycycline in children under 12. Regarding the reference provided, this will not be included in the evidence review as it is not a research study.
31	Royal Pharmaceutical Society	Guideline	5-6	Table 1-2	There is no mention of consideration of use of anti-influenza agents during the appropriate season, nor of influenza testing or vaccination – this should be added	Thank you for your comment. The committee discussed that it is good practice for clinicians to be aware of which flu strains are commonly circulating during the appropriate season and recommendation 1.1.1 states that local surveillance data (such as flu rates) should be taken account of when offering an antibiotic. Influenza vaccination is outside the remit of this guideline.
32	Royal Pharmaceutical Society	Guideline	8	2 onwards concerning CRB or CURB-65	Is the use of CURB-65 being mandated in secondary care? Some organisations, as part of a demand management exercise, have reduced the requesting of urea tests as many were unnecessary. This required the introduction of CRB-65 scoring for our in-patient and admitted population – are NICE suggesting that such organisations will now have to go back to requesting numerous urea assays with increased costs?	Thank you for your comment. The NICE guideline on pneumonia (CG191) recommends that if a person with community-acquired pneumonia presents to hospital, the risk of death should be determined using CURB65. CURB65 testing is indicated as a guide for determining severity in this antimicrobial prescribing guideline on community-acquired pneumonia, based on the recommendations in CG191.
33	Royal Pharmaceutical Society	Guideline	11	Committee discus	The rationale states “clinical judgement should be used when deciding when to stop antibiotic treatment, which should usually be	Thank you for your comment. The committee based the recommendation for 5 day course lengths of antibiotics across all severities of

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				sion box	after 5 days". How does this relate to the evidence reviewed which often looked at treatment courses of 7-14 days for both low and moderate-high severity infections? We agree that we should be aiming for shorter courses, but the guidance comes down heavily that therapy should stop after 5 days unless certain criteria are not met and we believe that those criteria should be more explicitly spelled out such as what are the BP, HR, RR & pO2 parameters that would allow early cessation? Also, the authors of the *Uranga* study say this in their discussion – "almost 80% of the patients received quinolones… …Hence the results probably cannot be extrapolated to other countries where B-lactams are widely used, such as the United Kingdom. They also included very few patients with severe disease (PSI class V) yet this guideline suggests a 5 day course for severe disease also. Recommendation for 5 day course of antibiotics is welcome but may be difficult to implement in some settings if patient packs do not align with this (many are 7 day course. *Clostridium difficile* infection is not mentioned and this is considered important as some broad spectrum antibiotics are recommended.	community-acquired pneumonia on 2 studies (Uranga et al. 2016 and Aliberti et al. 2017). Both studies compared strategies of stopping antibiotics after a 5 day course length if the person was clinically stable (according to physiological criteria) with stopping antibiotics based on physician judgement, as described in the committee discussion section on antibiotic course length. The committee recognised that in some individual circumstances a longer course may be required, therefore agreed to include a footnote in the antibiotic prescribing table for adults stating that antibiotics should be stopped after 5 days unless the person is not clinically stable, based on the presence of fever and other physiological criteria (based on the criteria used in the study by Uranga et al. 2016). The committee agreed that the specific criteria used in Uranga et al. 2016 would help guide decision making and have included this in the footnote. In children and young people, no evidence on specific review criteria was identified, therefore the committee agreed that the decision to continue antibiotics after a 5 day treatment course should be based on clinical judgment. The committee was aware of the limitations of the study by Uranga et al. 2016, but agreed that this was applicable to UK practice and people with all severities of community-acquired pneumonia. They also noted that there was supportive evidence provided by Aliberti et al. 2017. The committee agreed

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						that the footnote stating when antibiotics should be continued after 5 days was appropriate for safety netting people who will require longer course lengths. The committee recognised the issue with pack sizes, however agreed that a 5-day course length is still appropriate. The committee considered the risks of *Clostridium difficile* infection alongside the risk of harm from not adequately treating the infection. The committee discussion section has been updated to reflect this discussion.
34	Royal Pharmaceutical Society	Guideline	15	24	“Co-amoxiclav was significantly better than amoxicillin for improving cure rate” yet amoxicillin is the drug recommended in the guidance? Why is this?	Thank you for your comment. As described in the committee discussion section on choice of antibiotics in children with non-severe community-acquired pneumonia, the committee noted that the evidence showing co-amoxiclav was more effective than amoxicillin was from 1 small randomised controlled trial which showed a lower than expected response rate to amoxicillin, which may have been due to sub-therapeutic dosing. Therefore, the committee based the recommendation for amoxicillin as first choice antibiotic in children with non-severe community-acquired pneumonia on its experience of its effectiveness in current practice and that it is well tolerated.
35	Royal Pharmaceutical Society	Guideline	28	8 and Committee Discus	The Committee discussions on route suggest the evidence reviewed shows that oral antibiotics are as effective as continuous IV antibiotics in adults – yet the paper quoted to support this (Athanassa 2008) does not say	Thank you for your comment. The committee discussed the evidence from Lodha et al. 2013 on route of administration. This showed that in children with severe community-acquired pneumonia, oral antibiotics are more

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				sion Box	this at all – its conclusion is “”Early conversion to oral antibacterials seems to be as effective as continuous intravenous treatment in … moderate to severe CAP”, so does not provide support to the recommendation that severe CAP can be managed from the outset with oral therapy. In fact, the potential for death in patients with CURB-65 of 4 or more should prompt immediate IV therapy, and not consideration of oral administration. We would suggest that this recommendation for the oral route in all patients should be reconsidered.	effective than injectable antibiotics. The committee noted that there was no evidence identified on first-line intravenous antibiotics compared with oral antibiotics in adults. However, based on its experience, the principles of antimicrobial stewardship, and supported by the evidence in children, the committee agreed that adults with high-severity community-acquired pneumonia may be able to have oral antibiotics in certain circumstances, but that some people will require intravenous antibiotics and this decision should be based on clinical judgement. A footnote in the antibiotic prescribing table states that oral antibiotics should be given first-line if the severity of their condition does not require intravenous antibiotics.
36	UK Clinical Pharmacy Association	Guideline	5		For low severity CAP should IV be an option as this may inappropriately promote IV use? e.g. amoxicillin 500mg IV	Thank you for your comment. The committee agreed that some people cannot take oral medicines and therefore an option for intravenous route of administration is necessary for all severities of community-acquired pneumonia. However, the committee agreed that oral antibiotics are usually appropriate for low- and moderate-severity and non-severe community-acquired pneumonia and therefore simplified the antibiotic prescribing tables by removing reference to intravenous doses in these populations.
37	UK Clinical Pharmacy Association	Guideline	General		Recommendation for 5 day course of antibiotics is welcome but may be difficult to implement in some settings if patient packs	Thank you for your comment. The committee recognised the issue with pack sizes, however agreed that a 5 day course length is still appropriate.

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					do not align with this (many are 7 day course).	
38	UK Clinical Pharmacy Association	Guideline	General		Doxycycline may be a suitable treatment option but is not included.	Thank you for your comment. Doxycycline is included as an alternative antibiotic for low-severity community-acquired pneumonia. The committee also agreed that doxycycline is a reasonable alternative antibiotic choice for people with moderate-severity community-acquired pneumonia and have added this as an alternative option for this population.
39	UK Clinical Pharmacy Association	Guideline	General		Clostridium difficile infection is not mentioned and this is considered important as some broad spectrum antibiotics are recommended.	The committee considered the risks of *Clostridium difficile* infection alongside the risk of harm from not adequately treating the infection. The committee discussion section has been updated to reflect this discussion.
40	UK Clinical Pharmacy Association	Guideline	General		EUCAST evidence suggesting the need for increased doses (specifically co-amoxiclav/amoxicillin/levofloxacin).	Thank you for your comment. The committee agreed that it was appropriate to recommend the usual British National Formulary (BNF) doses for community-acquired pneumonia (or respiratory tract infections). For people with high-severity or severe community-acquired pneumonia, where a range of doses is given in the BNF, the committee agreed to recommend the higher dose, including for co-amoxiclav and levofloxacin. For amoxicillin in low- and moderate severity or non-severe community-acquired pneumonia, the lower dose has been included in the antibiotic prescribing tables, with a note to refer to the BNF(c) for higher doses.
41	UK Clinical Pharmacy Association	Guideline	5		New fluoroquinolone alerts and the use of levofloxacin.	Thank you for your comment. The committee was aware of the MHRA Drug Safety Update (2019) and agreed that the high risk of mortality without appropriate treatment in

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						people with high-severity community-acquired pneumonia outweighed the safety concerns.
42	UK Clinical Pharmacy Association	Guideline	6		Recommendation for doxycycline use in children – in practice doxycycline is not recommended even if child is > 12 years of age.	Thank you for your comment. The committee agreed that as doxycycline is included in the British National Formulary for Children (BNFc), for children aged 12 to 17, and based on their experience of current practice, it was appropriate to recommend doxycycline for this age range. Due to changes in the BNFc regarding the age restrictions for doxycycline, the committee also agreed to include a footnote linking to the BNFc, for appropriate use of doxycycline in children under 12.
43	UK Clinical Pharmacy Association	Guideline	7		Recommendation for double dose co-amoxiclav in children 1-5 years - in practice to aid compliance 5ml of the 250mg/5ml suspension is often prescribed. Appreciate this is not recommended in the BNF-C but should be considered as is common practice in paediatric centres. Where has the evidence for using double dose come from?	Thank you for your comment. The committee agreed that children with severe community-acquired pneumonia should be offered the double dose listed in the British National Formulary for Children (BNFc) for co-amoxiclav in respiratory tract infections. The committee agreed that 5 ml of 250/60 suspension could also be used to obtain the double dose listed in the BNFc and a footnote has been added explaining this is an option.
44	Neonatal and Paediatric Pharmacists Group	Summary	General		I know that NICE have reviewed the evidence, but the current NICE document 'Summary of antimicrobial prescribing guidance – managing common infections' https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/antimicrobial%20guidance/summary-antimicrobial-prescribing-guidance.pdf does use 7 -10 day antibiotic duration for severe CAP. Presumably NICE will also update this document in line with the guideline.	Thank you for your comment. The NICE/PHE summary of antimicrobial prescribing guidance will be updated to reflect the recommendations made in this antimicrobial prescribing guideline.

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45	Neonatal and Paediatric Pharmacists Group	Guideline	5-7		Should the duration of antibiotic be extended to 14 days if *Staphylococci* suspected (and also with addition of flucloxacillin if only on amoxicillin to begin with)?	Thank you for your comment. The committee agreed that some people, for example people with microbiology results which suggest an infection with an organism such as *Staphylococcus aureus*, may require a course length longer than 5 days. Therefore, the footnote suggesting when to stop antibiotic treatment has been updated to recommend not stopping if microbiology results suggest a longer course length is necessary. The committee was not able to make recommendations on choice of additional antibiotic treatment for every causative pathogen which may cause community-acquired pneumonia and decisions on such treatment should be based on clinical judgement.
46	Royal College of Physicians	General	General		The RCP is grateful for the opportunity to respond to the above consultation. In doing so we would like to endorse the response submitted by the British Thoracic Society (BTS). We have also liaised with our Joint Specialty Committee for Infectious Disease and would like to make the following comments.	Thank you for your contribution to this guideline.
47	Royal College of Physicians	General	General		In terms of treatment, the use and duration of use of macrolides could be more restrictive, partly because of the risk of driving antimicrobial resistance and partly because of drug interactions (mainly with statins). The evidence that macrolides, when given in addition to beta-lactams, improve outcomes is pretty scarce. The argument that they are needed for atypical organisms is weak as atypical pneumonia is relatively uncommon.	Thank you for your comment. The committee discussed the recommendations for offering macrolides for people with community-acquired pneumonia. The committee agreed that macrolides are an appropriate antibiotic class to provide cover for atypical pathogens in this population, given that fluroquinolones are associated with MHRA safety warnings. The committee agreed that the risk of drug interactions was limited as statin treatment

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						can usually be temporarily stopped during the course of antibiotics and that the risk of antimicrobial resistance was outweighed by the risk of harm from treatment with an ineffective antibiotic. Based on their experience, the committee noted that atypical pathogens are the causative organism in around 10 to 15% of moderate- to high-severity infections. The committee discussed that there was limited evidence on the effectiveness of dual therapy with a macrolide and therefore made recommendations based on their experience of which antibiotics would be most likely to cover the infective organisms. The committee agreed that people with low- and moderate-severity community-acquired pneumonia are at low risk of harm from not having atypical cover, but that if infection with an atypical pathogen is suspected in these populations, the option to provide atypical cover should be given. In people with high-severity community-acquired pneumonia, the committee agreed that the risk of harm from undertreatment of people infected with an atypical pathogen outweighed the risk of harm from broad spectrum, dual antibiotic treatment. The committee agreed that a 5 day course length was appropriate for all severities of community-acquired pneumonia, including for macrolide treatment.
48	Royal College of Physicians	General	General		Our experts believe the guidance should also emphasise the taking of blood cultures before administering antibiotics, especially in	Thank you for your comment. Recommendation 1.1.5 on microbiological testing cross references the NICE guideline

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					nosocomial pneumonia (some cases of pneumonia will be bacteraemic and some nosocomial cases might be misdiagnosed as pneumonia).	on pneumonia (CG191), which recommends taking blood samples from people with moderate- or high-severity community-acquired pneumonia. This antimicrobial prescribing guideline does not cover nosocomial pneumonia (please see related guidance on hospital-acquired pneumonia).
49	Royal College of Physicians	General	General		Our experts believe the suggestion about sending sputum samples should be removed. Sputum is rarely useful in the context of acute pneumonia, sputum assessment in the labs adds to workload without any useful information being provided and, if sputum tests are done, might lead to overuse of antibiotics.	Thank you for your comment. Recommendation 1.1.5 on microbiological testing cross references the NICE guideline on pneumonia (CG191), which recommends taking sputum samples from people with moderate- or high-severity community-acquired pneumonia. The committee discussed your comment but agreed that microbiological samples (for example, sputum samples) may also be beneficial in children and young people in hospital with community-acquired pneumonia with severe symptoms or signs or a comorbidity and for people in who symptoms or signs have not improved following antibiotic treatment (who have not already had microbiological tests performed). Therefore, only minor changes to clarify which children should have microbiological tests performed have been made.
50	British Thoracic Society	Guideline	General		Thank you for inviting comments from the British Thoracic Society.	Thank you for your contribution to the guideline.
51	British Thoracic Society	Guideline	General		Thank you for inviting comments from the British Thoracic Society.	Thank you for your contribution to the guideline.
52	British Thoracic Society	Guideline	2	1.1.1	We disagree with “Within 4 hours of **establishing** a diagnosis”. Surviving sepsis	Thank you for your comment. The committee agreed to amend the recommendations to

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					2018 bundle has antibiotics within 1hr. We note that there can be blind use of antibiotics in ED with “SIRS” patients having Tazocin without a diagnosis or thought. However, when there is an **established** diagnosis of pneumonia why is a 4 hour wait acceptable? Studies which looked at time to antibiotics with regards to outcome, tended to look at time from ED triage/arrival and not actual established diagnosis of pneumonia.	specify that antibiotic treatment should be started as soon as possible after establishing a diagnosis, and certainly within 4 hours. This recommendation is in line with the NICE guideline on pneumonia (CG191). The committee also agreed that for people with suspected sepsis and any of the high risk criteria for sepsis, antibiotics should be started within 1 hour, in line with the NICE guideline on sepsis (NG51).
53	British Thoracic Society		2	1.1.3	Rather than review IV antibiotics by 48 hours, suggest review of IV antibiotics daily for consideration of stepping down to oral administration.	Thank you for your comment. The committee agreed that the current wording allows for reviewing the use of intravenous antibiotics sooner than 48 hours, and that this it is good clinical practice to switch to oral antibiotics as soon as appropriate. This is in line with Public Health England guidance (Start smart then focus) and the NICE guideline on antimicrobial stewardship.
54	British Thoracic Society		5	1.2	We note that hospitals all had very clear Trust guidelines - should there be an acknowledgement of local guidelines in this section? Re: *“The committee agreed that when microbiological results are available, the antibiotic should be reviewed and changed according to results (for example, if bacteria are found to be resistant or atypical pathogens are not isolated), using a narrower spectrum antibiotic, if appropriate.*	Thank you for your comment. The recommendations made in this antimicrobial prescribing guideline are the national recommendations from NICE and Public Health England. The recommendations on antibiotic prescribing update and replace recommendations in the NICE guideline on pneumonia (2014). The recommendation to offer an antibiotic states that local antimicrobial resistance data should be taken into account. The committee agreed that the decision to change antibiotics according to results should be based on clinical judgement taking into account response and the risk of antimicrobial

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					If a patient is responding very well to a single-agent regime and micro reported “resistance” would people change according to a result? *Re:* *“Tendon damage (including rupture) has been reported rarely in people 18 receiving fluoroquinolones (BNF, December 2018)…* Should the risk with concurrent steroids be highlighted? Re: *“The committee noted that adults with high-severity community-acquired pneumonia will be managed in a high-dependency or an intensive care unit,…”* Many hospitals do not have HDU’s. They essentially have NIV units (likely inappropriate for CAP) and ICU admission is based on anticipated or actual need for organ support rather than severity of CAP.	resistance. Therefore, the committee agreed to amended the bullet in recommendation 1.1.10 to *consider* changing the antibiotic according to results. The safety of antibiotics section has been updated to include the MHRA Drug Safety Update (March, 2019), including the recommendation to avoid use with coadministration with corticosteroids. The statement on high-dependency or intensive care unit care for people with high-severity community-acquired pneumonia has been removed from the guideline.
55	British Thoracic Society	Guideline	5	Table 1	Consider putting doxycycline above macrolides for the alternative antibiotic choice as tetracyclines may be safer for various reasons (drug-drug interactions, cardiovascular risk etc). The order drugs are placed has a huge effect on prescription rates.	Thank you for your comment. The committee agreed that it was appropriate to list doxycycline first as an alternative antibiotic for adults with low-severity community acquired pneumonia. This change has been made to table 1.

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56	British Thoracic Society	Guideline	5	Table 1	Suggest NICE remove the “if atypical pneumonia suspect” from the alternative antibiotics for CURB65= 0 patients. The reliability of doctor suspicion to diagnose atypical pneumonia is unproven, so this guidance could lead to unnecessary overtreatment.	Thank you for your comment. The committee discussed the difficulties in diagnosing infection with an atypical pathogen and agreed to include a footnote to add some more guidance for when an atypical infection is more common. The committee agreed that if infection with an atypical pathogen is suspected in people with low-severity community-acquired pneumonia the option to provide atypical cover should be given. They agreed that the risk of harm from over treatment with inappropriate atypical cover is outweighed by the risk of harm from undertreatment in people with an atypical infection.
57	British Thoracic Society	Guideline	5	Table 1	The recommendation to treat severe CAP (CURB65 3-5) with 5 days of antibiotics is a surprise. There are occasions when this might be appropriate but we are surprised to see this recommendation made so strongly. The committee justification is based on the study by Uranga which is small and which included patients with mixed severity many of whom did not have severe CAP. The committee has not distinguished ICU patients here where there is limited evidence for short course therapy. 5 days may be appropriate for many patients with CAP and we support the intention to avoid excessive courses but feel there should be some caveats for high severity disease and specific organisms e.g. legionella.	Thank you for your comment. The committee discussed the specific population included in Uranga et al. 2016 and in the supportive evidence from Aliberti et al. 2017 and noted the lack of evidence in people being treated in intensive care units. The committee discussed that a 5 day course length may not be appropriate for all people with community-acquired pneumonia (for example people infected with *Legionella pneumophila*) and therefore included a footnote to state that antibiotics should be stopped after 5 days unless microbiological results suggest a longer course length is needed or the person is not clinically stable (based on physiological criteria).

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58	British Thoracic Society	Guideline	5	Table 1	We query amoxicillin 500mg for allcomers, and suggest that not 500mg -1g may be appropriate in higher severity?	Thank you for your comment. The recommended amoxicillin dose for moderate-severity community-acquired pneumonia is 500 mg. The table also states that higher doses can be used and refers to the BNF, where 500 mg to 1 g is recommended. Amoxicillin is not an antibiotic choice in high-severity community-acquired pneumonia.
59	British Thoracic Society	Guideline	5	Table 1	NICE states that for CURB65 2 either iv or oral. We suggest recommending oral unless that route is unavailable.	Thank you for your comment. The committee agreed that some people cannot take oral medicines and therefore an option for intravenous route of administration is necessary for all severities of community-acquired pneumonia. However, the committee agreed that oral antibiotics are usually appropriate for moderate-severity community-acquired pneumonia and therefore simplified the antibiotic prescribing table by removing reference to intravenous doses in this population.
60	British Thoracic Society	Guideline	6	Table 1	IV to oral switch is recommended as 48 hours. It is common to use clinical stability, which is often sooner and so could be changed to "as soon as is appropriate" or "when clinical improvement and normal temperature for 48h".	Thank you for your comment. The committee agreed that the current wording allows for reviewing the use of intravenous antibiotics sooner than 48 hours, and that it is good clinical practice to switch to oral antibiotics as soon as appropriate. This is in line with Public Health England guidance (Start smart then focus) and the NICE guideline on antimicrobial stewardship.
61	British Thoracic Society	Guideline	8	23	There is an error in the severity assessment section where CURB65 is put as age >65 years as one of the criteria when it should be age > or equal to 65.	Thank you for your comment. This has been amended throughout the guideline, evidence review and visual summary.

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62	British Thoracic Society	Guideline	9	4	The pneumonia severity index is mentioned in the text- this is a US scoring system that has never been used in the UK and we suggest removing it from the document as it could just cause confusion.	Thank you for your comment. The committee agreed that including the Pneumonia Severity Index (PSI) definition as a term used in the guideline is not appropriate and this has been removed from the guideline. However, it is appropriate to include reference to the PSI in the summary of the evidence and committee discussion where the evidence used this as the method of severity assessment.
63	British Thoracic Society	Guideline	21		There is a section on considerations by the committee where the committee noted that patients with high severity community-acquired pneumonia will be managed on an HDU or ICU. This is incorrect and the committee should be made aware that patients with CURB65 3-5 are, for the vast majority of cases, managed in a ward based setting. HDU and ICU care are reserved in the UK for patients with respiratory and circulatory failure/severe sepsis.	Thank you for your comment. This statement has been removed from the evidence review and the guideline.
64	British Thoracic Society	Guideline	21		p21 "Macrolides can be stopped when atypical infection is ruled out". How do they suggest doing this (legionella ag negative enough?)	Thank you for your comment. The recommendations for microbiological testing cross-refer to the recommendations in the NICE guideline on pneumonia (CG191). This recommends: “For people with moderate- or high-severity community-acquired pneumonia: • take blood and sputum cultures and • consider pneumococcal and legionella urinary antigen tests.” However, the committee discussed the difficulties in diagnosing atypical infection and therefore agreed that the decision to stop the macrolide should be reviewed based on

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						microbiological results instead of necessarily stepping down if atypical pathogens are not isolated. Therefore, clinical judgement can be used alongside the available microbiological test results to determine if stepping down from dual therapy is appropriate.
65	British Thoracic Society	Guideline	various		Legionella pneumophila (not pneumophilia) Mycoplasma pneumoniae (not pneumonia)	Thank you for your comment. This has been corrected in the guideline and the evidence review.
66	British Thoracic Society	Guideline	3	1.1.8	In 1.18 streamlining with a respiratory sample only is suggested, yet later in the document state "when microbiological results are available, the antibiotic should be reviewed and changed according to results (for example, if bacteria are found to be resistant or atypical pathogens are not isolated), using a narrower spectrum antibiotic, if appropriate". They should clarify whether they regard the antigen testing as suitable for streamlining or not.	Thank you for your comment. The recommendation on testing during reassessment has been updated to clarify that any microbiological test results can be used to review the choice of antibiotic and guide changing antibiotics.
67	British Thoracic Society		General		Should this document comment on empyema more? Some trusts will have antimicrobial guidance as well as highlighting the importance of drainage	Thank you for your comment. The antimicrobial prescribing guideline focuses on antimicrobial treatment for community-acquired pneumonia and does not cover complications associated with pneumonia.
68	Aspire Pharma	Draft guideline	5-7 (1.2 Choice of antibiotics)	Table 1 – 'Alternative antibiotics if low- and high-	This recommendation is not in line with guideline CG191, Pneumonia in Adults: Diagnosis and Management, which states that for low severity CAP, a macrolide should be used second line for patients who are allergic to penicillin – no macrolide preference is specified and states that for moderate to high severity CAP, a macrolide should be used in combination with a beta-lactam or	Thank you for your comment. The recommendations on antimicrobial therapy in the NICE guideline on pneumonia (CG191) will be updated and replaced by the recommendations made in this antimicrobial prescribing guideline. The committee discussed including azithromycin as an antibiotic choice, noting

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				severity, for penicillin allergy or if amoxicillin unsuitable'; 'Alternative antibiotics if moderate-severity, for penicillin allergy …'	amoxicillin if dual antibiotic therapy is required. Where clarithromycin IV is recommended, we consider that azithromycin IV should also be listed instead or at least that azithromycin or clarithromycin are the macrolides of choice. The evidence summary references a systematic review (page 28) showing no difference in clinical response in patients given oral azithromycin and clarithromycin for community acquired pneumonia, suggesting no clinical benefit of using one molecule over the other (Pakhale et. al. 2014). Equally, erythromycin was not showed to confer a significantly higher cure rate than azithromycin in children with community acquired pneumonia (evidence summary, page 42). Azithromycin requires once per day dosing as opposed to once every 12 hours dosing for clarithromycin. According to Appendix O of the NICE Pneumonia guideline, the cost of Klaricid IV (clarithromycin) is £18.90 per day whereas Zedbac IV (azithromycin) costs £9.50 per day, so use of azithromycin represents a significant saving. Additional benefits that have not been considered are as follows:	the evidence suggesting no difference in effectiveness compared with clarithromycin (in adults) and erythromycin (in children and young people), as well as the cost implications. The committee discussed that no evidence meeting the review protocol showing tolerability of azithromycin or differential selection of macrolide resistance was identified in the evidence review and the references highlighted here also do not meet the guideline review protocol (see below for reasons). The committee agreed that the risk of drug interactions was limited as often concomitant medication can be temporarily stopped during the course of antibiotics (such as statin treatment). The committee agreed that clinical judgement should be used to choose an alternative appropriate antibiotic in cases where other medication is being taken and cannot be temporarily stopped, which will result in a drug interaction with clarithromycin or erythromycin. The committee agreed that the potentially lower risks of drug interactions with azithromycin compared with other macrolides was outweighed by the long half-life of azithromycin, meaning that it has continued activity for some time following the end of the course. The committee also discussed that there are concerns around an increased emergence of antibiotic resistance with azithromycin compared with other antibiotics, centred around the issue of its

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					Tolerability Animal models suggest that azithromycin may be less pro-arrhythmogenic than clarithromycin or erythromycin (Milberg et al, 2002; Ohtani et al, 2000). 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). 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. Clinically, azithromycin has been shown to be the safest of the macrolides in terms of cardiac toxicity (Mortensen et.al, 2014, Guo et.al. 2010, Owens and Nolin 2006). In a study by Zimmermann et al (2001), intravenous site reactions were significantly lower with azithromycin compared with clarithromycin (P<0.05) and gastrointestinal adverse reactions were significantly lower with azithromycin compared with erythromycin (P<0.05). No participants discontinued on azithromycin, whereas 50% of participants discontinued on clarithromycin, and 8% of participants each discontinued on erythromycin and placebo. This study showed	long half-life. The committee discussion section has been updated to reflect this. Regarding the references highlighted: Abu-Gharbieh et al. (2004) *This publication will not be included in the evidence review as it does not meet the review protocol criteria, based on study type (narrative review article).* Altenburg J et al. (2011) *This publication will not be included in the evidence review as it does not meet the review protocol criteria, based on population (not pneumonia).* Amsden G et al. (2002) *This publication will not be included in the evidence review as it does not meet the review protocol criteria, based on population (not pneumonia).* Dancer S. (2007) *This publication will not be included in the evidence review as it does not meet the review protocol criteria, based on study type (commentary).* Guo D. et al. (2010) *This publication will not be included in the evidence review as it does not meet the review protocol criteria, based on study type (systematic review of both observational and*

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					azithromycin had better infusion site tolerability than clarithromycin and better gastrointestinal tolerability than erythromycin. ***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 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,	*controlled trials, randomised and non-randomised).* Malhotra-Kumar S et al. (2007) *This publication will not be included in the evidence review as it does not meet the review protocol criteria, based on population (not pneumonia).* Milberg P et al. (2002) *This publication will not be included in the evidence review as it does not meet the review protocol criteria, based on being a non-human study* Mortensen E et al. (2014) *This publication will not be included in the evidence review as it does not meet the review protocol criteria, based on study type (observational cohort study)* Ohtani H et al. (2000) *This publication will not be included in the evidence review as it does not meet the review protocol criteria, based on being a non-human study* Owens R and Nolin R. (2006) *This publication will not be included in the evidence review as it does not meet the review protocol criteria, based on study type (narrative review article).* Pakhale S et al. (2014)

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					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,	*This publication is included in the evidence review and was considered during guideline development.* Van Banbeke F and Tulkens P. (2009) *This publication will not be included in the evidence review as it does not meet the review protocol criteria, based on study type (narrative review article).* Zimmermann T et al. (2001) *This publication will not be included in the evidence review as it does not meet the review protocol criteria, based on population (not pneumonia).* Zuckerman J. (2004) *This publication will not be included in the evidence review as it does not meet the review protocol criteria, based on study type (narrative review article).*

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					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: 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. <u>References</u> Abu-Gharbieh, et al. (2004). Antibacterial macrolides: a drug class with a complex pharmacological profile. Pharmacological research, 50, 211-222. Altenburg J et al. (2011) Immunomodulatory effects of macrolide antibiotics-part 2: advantages and disadvantages of long-term, low-dose macrolide therapy. Respiration 81, 75-87. Amsden, G., et al. (2002). A study of the interaction potential of azithromycin and clarithromycin with atorvastatin in healthy volunteers. J. Clinical pharmacology, 42, 444-449. Dancer, S. (2007). Attention prescribers: be careful with antibiotics. Lancet, 369, 442-443. Guo D et al. (2010) The cardiotoxicity of macrolides: a systematic review. Pharmazie 65, 631-640.	

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					Malhotra-Kumar.S, et al. (2007). Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide- resistant steptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study. Lancet, 369, 482-90. Milberg et al (2002) Divergent proarrhythmic potential of macrolide antibiotics despite similar QT prolongation: fast phase 3 repolarization prevents early after depolarizations and torsade de pointes. The Journal of Pharmacology and Experimental Therapeutics, 303, 218-225. Mortensen E et al. (2014) Association of azithromycin with mortality and cardiovascular events among older patients hospitalised with pneumonia. Journal of American Medical Association 311(21), 2199-2208. Ohtani H., et al. (2000). Comparative pharmacodynamic analysis of Q-T interval prolongation induced by the macrolides clarithromycin, roxithromycin and azithromycin in rats. Antimicrobial agents and chemotherapy, 44(10), 2630-2637. Owens R.C. and Nolin, R. C. (2006). Antimicrobial-associated QT interval prolongation: Pointes of interest. Clinical practices, 43, 1603. Packhale et.al. (2014) Antibiotics for community-acquired pneumonia in adult outpatients. Cochrane Database of Systemic Reviews. Issue 10 Van banbeke, F., Tulkens, PM. (2009) Safety profile of the respiratory fluoroquinolone moxifloxacin: comparison with other	

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					fluoroquinolones and other antibacterial classes. Drug Safety, 32, 359-378 Zimmermann T et al. (2001) Comparative tolerability of intravenous azithromycin, clarithromycin and erythromycin in healthy volunteers: results of a double blind, double dummy, four way crossover study. Clinical Drug Investigation 21(8), 527-536. Zuckerman, J. (2004). Macrolides and ketolides: azithromycin, clarithromycin, telithromycin. Infectious Disease clinics of North America, 18, 621-649.	
69	Royal College of Paediatrics and Child Health (on behalf of the British Paediatric Respiratory Society)	NICE community acquired pneumonia	General		The reviewer agrees with the recommendations	Thank you for your comment.
70	Royal College of Paediatrics and Child Health (on behalf of the British Paediatric Respiratory Society)	NICE community acquired pneumonia	General		Overall, the guideline reflects clinical practice in children	Thank you for your comment.
71	Royal College of Paediatrics and Child Health (on behalf of the	NICE community acquired pneumonia	General		It was suggested that a standalone paediatric guideline would be more beneficial as being intertwined with the adult guideline can be confusing and may lead to mistakes	Thank you for your comment. The scope for antimicrobial guidelines, including community-acquired pneumonia, covers all people aged 72 hours and older. Separate recommendations and antibiotic prescribing

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	British Paediatric Respiratory Society)					tables have been made for children and young people with the aim that the target population for each recommendation is clearly defined.
72	Correvio Ltd.	Guideline	6, 14	Table 1 From line 4	The choice of using the indicated molecules for the treatment of adult patients at risk of severe symptoms may not take into account co-morbid conditions which may limit the use of certain molecules, as bactericidal and safer choices may be required. For example, specific subgroups of patients may benefit from newer molecules; in particular frail/elderly patients at risk of poor outcome. In the post-hoc exploratory study analysing data from two pivotal trials, ceftobiprole treated patients showed numerical superiority in overall at-risk populations subgroups, whereby differences in outcome (clinical cure at TOC, 30-day all-cause mortality, early clinical improvement) >10% in specific risk-groups were observed. Specifically, a between-treatment difference >10% in the proportion of patients with an early clinical improvement at Day 3 was observed in high-risk CAP patients aged 75 years or older, in patients with COPD at baseline, in ICU patients, and in patients with PORT risk score ≥4. All reported differences favoured ceftobiprole over the comparator (ceftriaxone ± linezolid). Furthermore, in both the subgroup of patients aged 75 years or older and patients with COPD at baseline, these treatment differences	Thank you for your comment. The committee agreed that the antibiotics recommended will be appropriate for most people with community-acquired pneumonia, however they were not able to make recommendations for every population, for example people with individual comorbidities. Clinical judgement should be used when offering antibiotic treatment and alternative antibiotics should be chosen if the options listed are not appropriate. The highlighted post-hoc analysis (Scheeren et al. 2019) will not be included in the evidence review as the 1 included primary study within this analysis applicable to community-acquired pneumonia is included in the evidence review (Nicholson et al. 2012). The committee discussed the evidence for ceftobiprole compared with ceftriaxone ± linezolid and agreed that none of the antibiotics included in this comparison are appropriate to recommend for treatment of community-acquired pneumonia. This is due to their broad-spectrum as well as the lack of evidence identified comparing either of these antibiotics to those currently used in practice.

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					were associated with 95% CI that did not cross zero (patients aged 75 years or older: treatment difference 16.3, 95% CI 1.8, 30.8; patients with COPD at baseline: treatment difference 20.1, 95% CI 8.8, 31.1). When stratified by causative pathogen, a between-treatment difference of >10% in the proportion of high-risk patients with an early clinical improvement at Day 3 in the CAP group was observed in patients with any S. pneumoniae (12.7%, favouring ceftobiprole; 95% CI − 6.4, 31.8). These treatment differences favoured ceftobiprole over the comparator. [Scheeren, et al. BMC Infect Dis 2019.] Treatment differences>10% in early clinical response when stratified by risk factor and causative pathogen for the CAP study, were observed in the PORT ≥IV group (11.9% favouring ceftobiprole; 95% CI − 1.2, 25.0) When analysed by causative pathogen and risk factor, treatment differences of >10% in clinical cure at TOC were observed in ICU patients in the CAP study (10.5%, favouring ceftobiprole; 95% CI − 15.2, 36.1) When stratified according to risk factor, a between-treatment difference of >10% in 30-day all-cause mortality was also observed in CAP patients treated in the ICU (− 11.5%; favouring ceftriaxone ± linezolid; 95% CI −	

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					23.8, 0.7) in the CE population. [Scheeren, et al. BMC Infect Dis 2019 ;19(1):195].	
73	Correvio Ltd.	Guideline	6 18 onwards	Table 1 Box	The NICE experts committee agrees on the choice of empirical therapy, and the use of the enlisted agents to cover for *S. pneumoniae* especially and pathogens more commonly associate with CAP. Nonetheless, we believe that the recommendations may imply there will be no place for molecules with activity on Gram-positive as well as on Gram-negative pathogens in a selected subgroup of patients. Risk-stratification is crucial to assess the correct use of molecules, whereby some patients may benefit from molecules with strong bactericidal activity on clinically relevant pathogens. In a recent surveillance study on respiratory-tract pathogens collected in the United Kingdom and Ireland during 2014–2015, ceftobiprole demonstrated potent in vitro activity against pathogens commonly associated with CAP, such as *S. pneumoniae*, *H. influenzae,* and *M. catarrhalis*. All *H. influenzae* isolates were susceptible to ceftobiprole. Susceptibility to ceftobiprole was also high in *S. pneumoniae* and *M. catarrhalis*, with susceptibility rates of 99.8% and 99.6%, respectively, suggesting a role for ceftobiprole as empirical treatment choice for patients with CAP, given its comprehensive activity against the most common causative Gram-positive and Gram-negative pathogens.	Thank you for your comment. The committee based the recommendations for antibiotic treatment of community-acquired pneumonia on the evidence available as well as their experience of which antibiotics target the most common causative organisms. The committee agreed that for most people with community-acquired pneumonia, the antibiotics recommended will be appropriate and were not able to make any further recommendations covering all individual populations. No evidence was identified comparing ceftobiprole to an antibiotic applicable to UK practice for the treatment of community-acquired pneumonia, therefore the committee agreed not to recommend this antibiotic. The reference provided (Santerre et al. 2018) will not be included in the evidence review as this is an *in vitro* study conducted on isolates from a general population of people with lower respiratory tract infections (not specifically community-acquired pneumonia).

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					Ceftobiprole was also active against all *S. aureus* isolates tested, including both MSSA and MRSA, as well as against *S. aureus* isolates resistant to other antimicrobial agents, such as ciprofloxacin (18.5% resistant strains) and erythromycin (20.8% resistant strains). Only vancomycin demonstrated similar susceptibility rates against all *S. aureus* isolates, MSSA, MRSA, and S. pneumoniae, susceptibility rates versus ceftobiprole observed in this were 100%, 100%, and 99.8% respectively [Santerre-Henriksen A, et al., Infect Drug Res 2018;11:1309-1320]. Similar susceptibility rates were reported in previous studies of 9,067 pathogens collected from hospitalized patients across the EU and Middle East in 2008 (CLASS study) as well as by SENTRY surveillance programmes, denoting low resistance potential. These results are also in line with a recent surveillance study of 12,240 bacterial pathogens collected from Europe, Turkey, and Israel during 2015, in which ceftobiprole susceptibility rates of 100%, 96.5%, and 99.3% were observed for MSSA, MRSA, and S. pneumoniae, respectively Susceptibility to ceftobiprole in P. aeruginosa isolates (N=214) in the current study amounted to 86.0%. [Santerre-Henriksen A, et al.Infect Drug Res 2018]. This supports the use of ceftobiprole against infection caused by pathogens commonly associated with lower-respiratory	

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					tract infections [Santerre-Henriksen A, et al., Infect Drug Res 2018;11:1309-1320].	
74	Correvio Ltd.	Guideline	6 9 18 onwards	Table 1 Line 27 Box	The bactericidal activity of the molecule should specifically be taken into account for the frail/elderly populations, who may benefit from a potent bactericidal molecule with an enhanced spectrum of activity (Gram-positive and Gram negatives) [Scheeren, et al. BMC Infect Dis 2019;19(1):195]. *S. pneumoniae* remains the major etiological cause of CAP, followed by *H. influenzae, S. aureus,* and *M. catarrhalis.* Nonetheless, *P. aeruginosa* and other gram-negative bacilli also cause CAP in frail/elderly subjects, with underlying comorbidities, such as COPD. Moreover, post-influenza CAP caused by *S. aureus* is higher during influenza outbreaks. Although the proportion of patients infected with pathogens such as mainly *P. aeruginosa* and MRSA not covered by standard empirical treatment is low, these pathogens are associated with high mortality and costs. [Falcó et al. Expert Opin Pharmacother. 2018;19(13):1503-1509] Severe CAP is frequently complicated by pulmonary and extra-pulmonary complications, including sepsis, septic shock, acute respiratory distress syndrome, and acute cardiac events, resulting in significantly increased intensive care admission rates and mortality rates. [Cillóniz C et al. PES Pathogens in Severe Community-Acquired Pneumonia.Microorganisms. 2019 12;7(2).]	Thank you for your comment. The committee based the recommendations for antibiotic treatment of community-acquired pneumonia on the evidence available as well as its experience of which antibiotics target the most common causative organisms. The committee agreed that for most people with community-acquired pneumonia, the antibiotics recommended will be appropriate and were not able to make any further recommendations covering all individual populations. No evidence was identified comparing ceftobiprole to an antibiotic applicable to UK practice for the treatment of community-acquired pneumonia, therefore the committee agreed not to recommend this antibiotic. The antimicrobial prescribing guideline focuses on antimicrobial treatment for community-acquired pneumonia and does not cover complications associated with pneumonia. Regarding the references highlighted: Scheeren et al. (2019) *This will not be included in the evidence review as the 1 included primary study within this analysis applicable to community-acquired pneumonia is included in the evidence review (Nicholson et al. 2012).*

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					Moreover, the incidence of CAP increases with age and is associated with an elevated morbimortality due to the physiological changes associated with aging and a greater presence of chronic disease [G et al. Rev Esp Geriatr Gerontol. 2014;49(6):279-91] This includes elderly/frail patients at risk of poor outcome, as reported in the study by the Scheeren group, where ceftobiprole was shown to offer potential beneficial effects in such cohorts both in outcome and mortality [Scheeren, et al. BMC Infect Dis 2019;19(1):195.]	Falcó et al. (2018) *This publication will not be included in the evidence review as it does not meet the review protocol criteria, based on study type (expert opinion article).* Callóniz et al. (2019) *This publication will not be included in the evidence review as it does not meet the review protocol criteria, based on study type (narrative review).* González Del Castilli et al. (2014) *This publication will not be included in the evidence review as it is not a research article (other guidance)*
75	Correvio Ltd.	Guideline	6	Table 1	We note that the choice of antibiotics offered in Table 1 may not exclude the development of potential C *difficile colonization* [Slimmings C. J Antimicrob Chemother 2014 ;69(4):881-91]. Agents with limited activity on *P. aeruginosa* may increase the risk of carbapenem-resistant *P. aeruginosa* colonization [Coppry J Antimicrob Chemother. 2019 Feb 1;74(2):503-510].	Thank you for your comment. The committee considered the risks of *Clostridium difficile* infection alongside the risk of harm from not adequately treating the infection. The committee discussion section has been updated to reflect this discussion. The committee also discussed carbapenem-resistant *P. aeruginosa* colonisation and agreed that this was very rare in community-acquired pneumonia and that this antimicrobial prescribing guideline could not cover all individual circumstances. Regarding the references highlighted: Slimmings and Riley (2014)

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						This publication will not be included in the evidence review based on the population (people with hospital-acquired infections) Coppry et al. (2019) *This publication will not be included in the evidence review based on publication type (case-control study)*
76	Public Health England	Guideline	2	28	Public Health England knows that 20% of Community Acquired Pneumonia (CAP) cases are viral, so we are surprised by the recommendation to give antibiotics within four hours of diagnosis for a young, otherwise healthy patient with low-severity CAP. There should be a good argument for delayed prescriptions in that situation.	Thank you for your comment. The committee recognised that the cause of community-acquired pneumonia can be viral infection. The committee discussed the difficulties with accurately diagnosing viral pneumonia, and the potential risk of harm from not giving an antibiotic to people with community-acquired pneumonia. They also noted that no evidence comparing antibiotics to placebo was identified and that the clinical success rates with antibiotics were generally high. Therefore, the committee agreed that antibiotics should be offered for all people with community-acquired pneumonia. However, the committee agreed to make a recommendation that during reassessment, healthcare professionals should be aware of non-bacterial causes of community-acquired pneumonia, such as flu.
77	Public Health England	Guideline	10	Committee discussions	The Committee's discussions appear to be entirely around *which* antibiotic to prescribe rather than *whether* to prescribe, and that the wider pneumonia diagnosis/management guidance is much the same in that regard.	Thank you for your comment. The committee discussion section has been updated to reflect the discussion around viral infection and the decision to offer all people with community-acquired pneumonia an antibiotic.