Managing Common Infections

Clostridioides difficile infection: antimicrobial prescribing

Stakeholder comments table

21/01/2021 – 17/02/2021

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01	NHS Kent & Medway CCG	Choice of Antibiotic for treatment of CDI case	5	19	Metronidazole is no longer recommended and Fidaxomicin is now 2nd choice, depending upon patient status. This may be challenging in primary care because most GPs are unfamiliar with Fidaxomicin and have limited experience of using it and Vancomycin. Our Formularies at the moment list Metronidazole as first line, Vancomycin 2nd line if severe, type 027 or recurrent and Fidaxomicin for recurrent or 2nd line. Most GPs follow microbiology advice which is normally Vancomycin for our local trusts if patient`s case is problematic. If initiating within primary care usually metronidazole.	Thank you for your comment. The committee recognised that there are some implementation challenges for this guideline. Local health organisations, health and social care practitioners and other stakeholders will need to work collaboratively to ensure that appropriate treatment is available in primary care for people with suspected or confirmed *C. difficile* infection. NICE are working with other national stakeholders such as NHS England and Improvement (including procurement teams) to support implementation of the guideline. From their experience, the committee agreed that it was uncommon for people to present in the community with *C. difficile* infection, with GP committee members seeing very few cases. They recognised the importance of additional support for primary care prescribers who may be unfamiliar with the recommended antibiotics. Following discussion, they agreed that for people in the community, prescribers should consider seeking

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						prompt specialist advice from a microbiologist or infectious diseases specialist before starting treatment, and this has been added to the recommendation. The use of metronidazole was one of the options tested in the cost-effectiveness modelling used to underpin this guideline. When the costs of rehospitalisation were included in the analysis, the committee agreed the results were clear that vancomycin was a more cost-effective first-line treatment than metronidazole, and that it was dominant in most scenarios (meaning the use of vancomycin is both less costly and more effective than the use of metronidazole). These results are based on the clinical evidence review, which showed that metronidazole has both lower initial cure rates and higher recurrence rates than vancomycin. Considering all this evidence, the committee concluded that it was appropriate to retain the recommendation for vancomycin to be the first-line antibiotic of choice.
02	NHS Kent & Medway CCG	PPI Use	9	17	I have found when reviewing notes of patients who have tested positive for c. difficle that not a lot of consideration is given in primary care to stopping PPIs. Some more knowledgeable practitioners will stop PPI and note in PMR. However, unless specifically required eg in Barretts etc, patients are left on PPIs. It would be a good step to raise awareness of reviewing need for PPIs overall	Thank you for your comment. This is reflected in the guideline which recommends that the need to continue any treatment with proton pump inhibitors is reviewed.

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03	NHS Kent & Medway CCG	Antimotility Drug Use	3	18	There is a need to raise awareness of stopping or not initiating any antimotility drugs such as Loperamide if CDI case is suspected. We often see such drugs used, sometimes as a norm, despite CCG guidance.	Thank you for your comment. The recommendation has been amended to include reviewing the need to continue treatment with other medicines with gastrointestinal activity or adverse effects, such as laxatives. This includes antimotility medicines. There is also a recommendation to not offer antimotility medicines, such as loperamide, because they slow down the action of the gut and can lead to *C. difficile* toxins being retained for longer.
04	NHS Kent & Medway CCG	Review	12	22	It would be good practice to review midway through the expected course of any necessary antibiotic treatment for a clinical problem, the need for continuing the course and definitely not start antibiotics (Vancomycin etc) until CDI case has been confirmed. I think that dental prescribing needs to be considered within this guidance. Dentists can be high users of CDI promoting antibiotcs eg Clindamycin. Some reference to allay this could be added and the dentist s sent final guidance (I realise they will not be treating the patient for CDI but some background information may be useful)	Thank you for your comment. The committee recognised that people in hospital with *C. difficile* infection would be reviewed on a regular basis, at least daily. For people in the community, reassessment would be needed if symptoms or signs do not improve as expected or worsen rapidly or significantly at any time. The recommendation has been amended to reflect this. The committee agreed that antibiotic treatment should be started when a diagnosis of *C. difficile* infection is suspected or confirmed. Following discussion, they agreed that for people in the community, prescribers should consider seeking prompt specialist advice from a microbiologist or infectious diseases specialist before starting treatment, and this has been added to the recommendation. If subsequent stool

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						sample tests to not confirm *C. difficile* infection, stopping these antibiotics should be considered. Following good prescribing practice and antimicrobial stewardship is outside the scope of this guideline, including for dental prescribing. The guideline now signposts to other relevant national guidance in the 'Preventing *C. difficile* infection' section, which cover these aspects – Public Health England's guidance on *C. difficile* infection: how to deal with the problem, NICE's guidance on healthcare-associated infections and NICE's guidance on antimicrobial stewardship.
05	NHS Kent & Medway CCG				Difficult for me to comment on the practice of other GP's, I have not had the pleasure of reviewing any. From a clinical point of view - I would not prescribe antibiotics for diarrhea without bacteriological evidence, anti-motility drugs are not helpful in infective diarrhea and I do not use them for this. It would be really easy to put a note on the microbiology report to remind clinicians to consider stopping PPI's and review any other antibiotics. It would also be reasonable to suggest, direct, insist that clinicians discuss treatment with a microbiologist prior to starting treatment for C.Diff? I guess there may be a few GP's that might just start metronidazole for C Diff without seeking advice!!	Thank you for your comment. Diagnosis of *C. difficile* infection is outside the scope of this guideline. Users are signposted to Public Health England's guidance on diagnosis and reporting. The committee agreed that antibiotic treatment should be started when a diagnosis of *C. difficile* infection is suspected or confirmed. Following discussion, they agreed that for people in the community, prescribers should consider seeking prompt specialist advice from a microbiologist or infectious diseases specialist before starting treatment, and this has been added to the recommendation.

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						Other comments about the need to review proton pump inhibitors and not using antimotility medicines are covered within the recommendations. The use of metronidazole was one of the options tested in the cost-effectiveness modelling used to underpin this guideline. When the costs of rehospitalisation were included in the analysis, the committee agreed the results were clear that vancomycin was a more cost-effective first-line treatment than metronidazole, and that it was dominant in most scenarios (meaning the use of vancomycin is both less costly and more effective than the use of metronidazole). These results are based on the clinical evidence review, which showed that metronidazole has both lower initial cure rates and higher recurrence rates than vancomycin. Considering all this evidence, the committee concluded that it was appropriate to retain the recommendation for vancomycin to be the first-line antibiotic of choice.
06	County Durham & Darlington NHS Foundation Trust	Evidence Review	3	18	Should also include anti-spasmodics like Hyoscine butylbromide (Buscopan) and Opiates for pain control (Codeine phosphate and morphine derivatives)	Thank you for your comment. The recommendation has been amended to include reviewing the need to continue treatment with other medicines with gastrointestinal activity or adverse effects, such as laxatives. This includes antispasmodic and opiate medicines.
07	County Durham & Darlington	Evidence Review	5	10	The referral should also include a Gastroenterologist, since some patients may	Thank you for your comment. A recommendation has been added to

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	NHS Foundation Trust				need a flexible sigmoidoscopy and assessment for toxic megacolon.	ensure people in hospital with suspected or confirmed *C. difficile* infection have care from a multidisciplinary team that includes a gastroenterologist, as needed.
08	County Durham & Darlington NHS Foundation Trust	Evidence Review	6	Table	Recurrence of C. diff infection should be treated with vancomycin for mild and moderate episodes and with Fidaxomicin for severe episodes. This needs to be clarified in the table as Vancomycin (for mild and moderate infection) or Fidaxomicin (for severe infection)	Thank you for your comment. The committee recognised that the choice of antibiotic for a recurrent infection may depend on a range of factors. The committee agreed it was appropriate for both vancomycin and fidaxomicin to be first-line options for further episodes, with the choice coming down to an individualised patient decision based around severity, the risk of additional recurrences (which increases after each recurrent episode) and the time period between recurrences. The committee favoured fidaxomicin for more severe, more recent or multiple recurrent episodes, but felt vancomycin would be suitable for less severe or first recurrent episodes, or if there had been a long period of time between episodes. The prescribing table (table 1) has been amended to reflect this change.
09	County Durham & Darlington NHS Foundation Trust	Evidence Review	7	14-18	Other parameters of severity such as elevated lactate, low serum albumin and signs of peritonitis should also be mentioned	Thank you for your comment. The definition of severe *C. difficile* infection is from Public Health England's updated guidance on the management and treatment of *C. difficile* infection. This guideline on *C. difficile* infection: antimicrobial prescribing will update any Public Health England guidance recommendations on treating *C. difficile*

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						infection. Other aspects of these guidelines will be retained, for example recommendations on diagnosis and reporting. NICE will work closely with Public Health England to make sure this is clear for users.
10	County Durham & Darlington NHS Foundation Trust	Evidence Review	7	19-20	The term life threatening should be omitted and the characteristics included in Severe C. diff. This is also in keeping with international definitions such as in the ESCMID Guidelines (Debast et al Clin Microbiol Infect 2014;20:1-26.	Thank you for your comment. The definitions of severe and life-threatening *C. difficile* infection are from Public Health England's updated guidance on the management and treatment of *C. difficile* infection. The NICE guideline will update any Public Health England guidance recommendations on treating *C. difficile* infection. Other aspects of these guidelines will be retained, for example recommendations on diagnosis and reporting. NICE will work closely with Public Health England to make sure this is clear for users.
11	County Durham & Darlington NHS Foundation Trust	Evidence Review	11	24	Also include hyoscine butylbromide (Buscopan) and opiates.	Thank you for your comment. The recommendation has been amended to include reviewing the need to continue treatment with other medicines with gastrointestinal activity or adverse effects, such as laxatives. This includes antimotility and opiate medicines.
12	British Society of Gastroenterology				They should include the following in their "Terms used in this guidance section": relapse, recurrence, probiotic, prebiotic. They use these terms in their recommendations but their definitions are buried somewhat,	Thank you for your comment. These terms have been added to the 'Terms used in the guideline' section.

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					particularly for the lay audience they include in their intended readership.	
13	British Society of Gastroenterology				vancomycin levels for patients with inflammatory intestinal disorders – I have not come across this before-is this evidence based? I could not find any	Thank you for your comment. Monitoring vancomycin serum concentrations after oral administration in people with inflammatory intestinal disorders is advised in the BNF information on vancomycin and the vancomycin summary of product characteristics.
14	Aneurin Bevan University Healthboard	Visual Summary	1	General	Suggest add to prescribing considerations information to review the need for continuing any existing laxatives and prokinetics as well. It would also be useful to add information around to hold, or not hold, immunomodulatory agents	Thank you for your comment. The recommendation has been amended to include reviewing the need to continue treatment with other medicines with gastrointestinal activity or adverse effects, such as laxatives. The committee recognised the importance of reviewing medicines. However, they did not want to give more specific details, as this may be interpreted as an exhaustive list of medicines. This would need to be based on clinical judgment.
15	Aneurin Bevan University Healthboard	Visual Summary	General	General	It would be useful to add assessment of severity of infection to this document	Thank you for your comment. The visual summary has 'severity of infection' included as the second bullet point under the 'Assess' heading.
16	Aneurin Bevan University Healthboard	Guideline	3	8	Suggests using the rectal route as an alternative route of administration. Can some detail please be added on how this is to be done. The practical advice on how to administer was based on historic papers using a foley catheter which is no longer a viable method.	Thank you for your comment. The committee agreed that it was beyond the scope of the guideline to give specific details about administering medicines via alternative enteral routes, such as the rectal route. However, following stakeholder consultation they agreed that for people who cannot take oral medicines, specialist advice should be sought from a

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						gastroenterologist or pharmacist about alternative enteral routes for antibiotics. This has been added to the recommendation.
17	Aneurin Bevan University Healthboard	Guideline	4	9	Recommendation to reassess patients at 3-5 days after starting treatment. While this would be easily achieved if the patient remains in secondary care setting this would be more challenging in a primary care setting	Thank you for your comment. The committee recognised that people in hospital with *C. difficile* infection would be reviewed on a regular basis, at least daily. For people in the community, reassessment would be needed if symptoms or signs do not improve as expected or worsen rapidly or significantly at any time. The recommendation has been amended to reflect this, and the 3 to 5 day time period has been removed.
18	Aneurin Bevan University Healthboard	Guideline	4	9	Recommendation to reassess patients at 3-5 days after starting treatment. It should be made clear that resolution of diarrhoeal symptoms by this reassessment may not have happened and that this alone should not be a reason to change treatment at this point. Without this clarification it may lead to an increase in early switching to fidaxomicin.	Thank you for your comment. The committee agreed that resolution of diarrhoea may not happen by day 3 to 5. This has been clarified in the prescribing table (table 1) which states 'Use clinical judgement to determine whether antibiotic treatment for C. difficile infection is ineffective. It is not usually possible to determine this until day 7 because diarrhoea may take 1 to 2 weeks to resolve'. The recommendation on reassessment has been amended to remove the 3 to 5 day time period.
19	Aneurin Bevan University Healthboard	Guideline	11	14	FMT currently sits higher in the treatment pathway within our healthboard. While there remain issues of access and resource for this treatment option, including this as a treatment option could highlight that wider resource is needed.	Thank you for your comment. The committee agreed that the recommendation reflects the evidence for faecal microbiota transplant (FMT), although the recommendation wording has now been amended for greater clarity.

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20	Aneurin Bevan University Healthboard	Visual Summary	General	General	The wording of "do not routinely offer probiotics in people taking antibiotics" may cause people to consider this as an option again despite the lack of evidence.	Thank you for your comment. The committee agreed that there is some evidence (with many limitations) of a small effect with probiotics in preventing *C. difficile* infection. However, because of concerns about the evidence base they could not identify any scenario when the use of probiotics could be recommended in people taking antibiotics. Following stakeholder consultation, the recommendation has been amended so that it focuses on the advice given to people and states 'Do not advise people taking antibiotics to take prebiotics or probiotics to prevent *C. difficile* infection'.
21	Aneurin Bevan University Healthboard	Guideline	3	9	It is useful to have the recommendation around monoclonal antibodies included.	Thank you for your comment.
22	Aneurin Bevan University Healthboard	Evidence	48	40	It is very useful to have the economic modelling to support and inform local decisions	Thank you for your comment and your support for the work that has been done.
23	BNF Publications	Guideline	5	19	The oral vancomycin dosing recommended in Table 1 for adults is more restrictive than the dosing currently recommended in the BNF, which follows licensed dosing. The reasons for this choice of dose are set out in the rationale on the choice of antibiotic (p17 line 24) which is helpful, and when the guidance is published we would aim to amend BNF dosing to follow the NICE dosing. This would however mean that adult dosing in the BNF will follow NICE's restricted dosing, but children's dosing in the BNFC will still be based on licensed dosing. This is particularly	Thank you for your comment. The committee discussed the treatment of *C. difficile* infection in children and young people at length. As this is very rare, they did not want to include a prescribing table for children and young people (and therefore dosage information is not given). However, they agreed that the dosage of vancomycin for young people aged 12 to 17 years would not be expected to exceed the dosage recommended in adults. NICE will work with BNF to ensure this is reflected in the BNF content.

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					an issue for the 12-17 year old age bracket, where dosing for this age bracket could be higher than that used in adults, and would include a tapering or pulse regimen for recurrent infection (which is not included in the draft NICE guidance). We are concerned that these discrepancies could cause confusion in practice. Note that the draft NICE guidance (page 5, lines 14-16) suggests that the licensed indications for antibiotics should be taken into account when prescribing antibiotics for children and young people.	Following stakeholder consultation, in addition to seeking specialist advice, a specialist option (agreed by committee consensus) has been added to the prescribing table for treating *C. difficile* infection. For an infection that has not responded to first- and second-line antibiotics, higher doses of oral vancomycin could be used (up to 500 mg) with or without intravenous metronidazole. For a life-threatening infection, high-dose (500 mg) oral vancomycin with intravenous metronidazole is included. The committee were aware that vancomycin is licensed to be given in a tapered or pulsed regimen and agreed this was also one of a number of options that specialists could consider if standard antibiotic treatment was unsuccessful. However they did not include a tapered or pulsed regimen of vancomycin in the prescribing table (table 1) because its use was limited in the evidence review to studies in which there was co-administration of faecal microbiota transplant.
24	Royal College of Pathologists	Guideline	2	13	Use of laxatives is important both in determining if new onset diarrhoea and as a risk factor for development of C difficile diarrhoea. There does not seem to have been any discussion of laxatives as a risk.	Thank you for your comment. The recommendation has been amended to include reviewing the need to continue treatment with other medicines with gastrointestinal activity or adverse effects, such as laxatives.
25	Royal College of Pathologists	Guideline	3	4	Stopping treatment antibiotic alone is often adequate treatment	Thank you for your comment. The committee agreed that antibiotic treatment

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						should be started when a diagnosis of C. difficile infection of any severity is suspected or confirmed. The committee discussed that in some people, symptoms may resolve without treatment but agreed there is no way of identifying who these would be. Following discussion, they agreed that for people in the community, prescribers should consider seeking prompt specialist advice from a microbiologist or infectious diseases specialist before starting treatment, and this has been added to the recommendation. If subsequent stool sample tests to not confirm C. difficile infection, stopping these antibiotics should be considered.
26	Royal College of Pathologists	Guideline	3	11	Referring to 'antibiotics' could be confusing when oral vancomycin or similar is intended not the antibiotic that caused the problem	Thank you for your comment. All recommendations including antibiotics have been checked to make sure this is clear and amended as appropriate.
27	Royal College of Pathologists	Guideline	6	1	Agree fidaxomicin should be used for first relapse but many pharmacy groups restrict due to cost to more chronic infection	Thank you for your comment. The committee noted the higher price of fidaxomicin, but they also noted the evidence that it was associated with lower rates of relapse/recurrence. Given that people who have experienced a single relapse are at considerably increased risks of further relapses, the committee were confident that the use of fidaxomicin would be cost-effective in this population. The committee also hope the cost-effectiveness work done for this guideline will help to

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						encourage groups to make fidaxomicin available in those situations where it is clinically appropriate.
28	Royal College of Pathologists	Research	7	1	There are published studies but low quality. However efficacy is expected to be similar to vancomycin.	Thank you for your comment. The committee's recommendations are based on the best available clinical and cost effectiveness evidence. They were concerned about the extensive limitations of the 2 small studies of teicoplanin included in the network meta-analysis, both of which were at considerable risk of bias. The committee were also aware of the limited clinical experience with using teicoplanin in the UK for *C. difficile* infection. They concluded that there was not enough clinical evidence to recommend it and further research was needed, so made a recommendation for research.
29	Royal College of Pathologists	Guideline	17	17	IV metronidazole is used but rarely effective in practice	Thank you for your comment. Following stakeholder consultation, in addition to seeking specialist advice, a specialist option (agreed by committee consensus) has been added to the prescribing table for treating *C. difficile* infection. For an infection that has not responded to first- and second-line antibiotics, up to 500 mg oral vancomycin with or without intravenous metronidazole is included. For a life-threatening infection, high-dose (500 mg) oral vancomycin with intravenous metronidazole is included.
30	Royal College of Pathologists	Guideline	19	1	Infection control procedures and antimicrobial stewardship are the most important	Thank you for your comment. Infection control procedures and antimicrobial

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					preventive measures but are not considered. A discussion at least is needed, although there is an assessment in the following Evidence Review.	stewardship is outside the scope of this guideline. The guideline now signposts to other relevant national guidance in the 'Preventing *C. difficile* infection' section, which cover these aspects – Public Health England's guidance on *C. difficile* infection: how to deal with the problem, NICE's guidance on healthcare-associated infections and NICE's guidance on antimicrobial stewardship.
31	Royal College of Pathologists	Guideline	21		Fidaxomicin is used first line in some hospitals as well as a treatment for relapses but in others is prohibited on cost grounds.	Thank you for your comment. The cost-effectiveness modelling undertaken for this guideline was designed to address precisely this known variation in practice. The results of that modelling were that vancomycin was the most cost-effective first-line treatment for an initial infection, but there was a clear place for fidaxomicin where either vancomycin has not been effective, or where a person has suffered a relapse after initial vancomycin treatment.
32	Royal College of Pathologists	Evidence review	9	19	C difficile diarrhoea is the most common infective cause of diarrhoea in hospital patients.	Thank you for your comment. This has not been added to the evidence review as we are not clear about the evidence supporting this statement.
33	Royal College of Pathologists	Evidence review	10	16	The Cochrane review on stewardship (P Davey) should be included for practice recommendations.	Thank you for your comment. The NICE guideline on antimicrobial stewardship (NG15) recommends the techniques to improve antibiotic stewardship reported in the Davey et al. 2017 Cochrane review. The Cochrane (2017) review was considered as part of the NICE Surveillance report (2018) for NG15. Antimicrobial stewardship is one of the

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						main aims of the Managing Common Infections programme and this guideline now signposts to other relevant national guidance in the 'Preventing *C. difficile* infection' section, which cover these aspects – Public Health England's guidance on *C. difficile* infection: how to deal with the problem, NICE's guidance on healthcare-associated infections and NICE's guidance on antimicrobial stewardship.
34	Royal College of Pathologists	Evidence review	29	37	There are other oral teicoplanin C difficile studies: Wenisch (randomised) Clin Infect Dis 1996 22 813-8; De Lalla JAC 1989 23 131-42; De Lalla AAC 1992 36 2192-6; Scand J Infect Dis 1994 26 309-16	Thank you for comment. Please note that these studies are not eligible for inclusion as they fall outside the date limits set in the review protocol (not earlier than year 2000) agreed by the guideline committee (see appendix B in the evidence review). However, both Wenisch et al. 1996 and De Lalla et al. 1992 are included in the network meta-analysis by Beinortas et al. 2018.
35	Royal College of Pathologists	Evidence review	37	6	difficile not Difficile	Thank you for your comment. This has been corrected.
36	Royal College of Pathologists	Evidence review	39	40	Infection control and stewardship of antibiotics should be the first measures in prevention and less emphasis on the use of antibiotics to treat or prevent C difficile especially if mild disease.	Thank you for your comment. Infection control procedures and antimicrobial stewardship is outside the scope of this guideline. The guideline now signposts to other relevant national guidance in the 'Preventing *C. difficile* infection' section, which cover these aspects – Public Health England's guidance on *C. difficile* infection: how to deal with the problem, NICE's guidance on healthcare-associated

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						infections and NICE's guidance on antimicrobial stewardship.
37	Faculty of Homeopathy	Guideline	6	7	Probiotics have the highest quality evidence among cited prophylactic therapies. For example, two studies cited here - Gao, X.W., Mubasher, M., Fang, C.Y., Reifer, C. and Miller, L.E., 2010. Dose–Response Efficacy of a Proprietary Probiotic Formula of Lactobacillus acidophilus CL1285 and Lactobacillus casei LBC80R for Antibiotic-Associated Diarrhea and Clostridium difficile-Associated Diarrhea Prophylaxis in Adult Patients. American Journal of Gastroenterology, 105(7), pp.1636-1641. Bio-K (3 species of Lactobacillus) prophylaxis was associated with a lower incidence of antibiotic or *C. difficile* associated diarrhoea (CDAD) in a phase 3 trial (randomised double blinded RCT) Ouwehand, A.C., DongLian, C., Weijian, X., Stewart, M., Ni, J., Stewart, T. and Miller, L.E., 2014. Probiotics reduce symptoms of antibiotic use in a hospital setting: a randomized dose response study. Vaccine, 32(4), pp.458-463. The World Gastroenterology Organisation Global Guidelines summarise the evidence for probiotics in the prevention of CDAD and recommended doses based on the trial data - Guarner, F., Khan, A.G., Garisch, J., Eliakim, R., Gangl, A., Thomson, A., Krabshuis, J., Lemair, T., Kaufmann, P., De Paula, J.A. and Fedorak, R., 2012. World gastroenterology organisation global guidelines: probiotics and	The committee agreed that there is some evidence (with many limitations) of a small effect with probiotics in preventing *C. difficile* infection. However, because of concerns about the evidence base they could not identify any scenario when the use of probiotics could be recommended in people taking antibiotics. Following stakeholder consultation, the recommendation has been amended so that it focuses on the advice given to people and states 'Do not advise people taking antibiotics to take prebiotics or probiotics to prevent *C. difficile* infection'. The studies by Gao et al. 2010 and Ouwehand et al. 2014 are included in the Cochrane review by Goldenberg et al. 2017. The Guidelines produced by the World Gastroenterology Organisation (WGO; Guarner et al. 2011) are not eligible for inclusion (not a randomised controlled trial or systematic review). The WGO guideline also excludes more recent trials included in the Cochrane review (Goldenberg et al. 2017). Please note the WGO 2017 guidance is the current version.

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					prebiotics october 2011. Journal of clinical gastroenterology, 46(6), pp.468-481. A recent review article highlights robust evidence to support the use of probiotics and prebiotics to improve symptomology and have a meaningful effect on reducing pathology and even saving lives. The review considers the prevention of Clostridium difficile-associated diarrhoea as a clinical indication for the use of probiotics. Sanders, M.E., Merenstein, D.J., Reid, G., Gibson, G.R. and Rastall, R.A., 2019. Probiotics and prebiotics in intestinal health and disease: from biology to the clinic. Nature reviews Gastroenterology & hepatology, 16(10), pp.605-616.	The study by Sanders et al. 2019 is not an eligible study type (not a randomised controlled trial or systematic review).
38	Faculty of Homeopathy	Guideline	29	9	The Goldenberg et al (2017) review analysed 31 studies (n=8672) and showed probiotics demonstrate a statistically significant reduction in the incidence of CDAD (1.5% vs 4% in placebo/control), NNT = 42. Therefore, moderate quality evidence supports a large protective effect for probiotics (e.g. S. boulardii or L. acidophilus plus L casei at a dose of 10 to 50 billion CFUs per day) in preventing CDAD. The authors did conduct sensitivity and post hoc subgroup analyses to explore the impact of missing data and heterogeneity. The results suggest probiotics may be more effective for people with a higher baseline risk of CDAD (> 5% risk; NNTB = 12; moderate quality evidence) than for people with a lower baseline risk of CDAD (< 5% risk).	The committee agreed that there is some evidence (with many limitations) of a small effect with probiotics in preventing *C. difficile* infection. However, because of concerns about the evidence base they could not identify any scenario when the use of probiotics could be recommended in people taking antibiotics. Following stakeholder consultation, the recommendation has been amended so that it focuses on the advice given to people and states 'Do not advise people taking antibiotics to take prebiotics or probiotics to prevent *C. difficile* infection'. In Goldenberg et al. 2017, the baseline risk in many of the included studies exceeds the baseline risk of *C. difficile* infection

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					The review concludes 'Stated in absolute terms, probiotic prophylaxis would prevent 85 Clostridium difficile-associated diarrhoea episodes per 1000 patients at high risk of C. difficile diarrhoea. Although adverse effects were reported among included trials, there were more adverse events among the patients in the control groups. The short- term use of probiotics appear to be safe and effective when used as an adjunct to antibiotics in immunocompetent patients.' 'probiotics are superior to placebo or no treatment for preventing Clostridium difficile-associated diarrhoea and, despite the need for further research, hospitalized patients, particularly those at high risk of CDAD, should be informed of the potential benefits and harms.' The authors conclusions on implications for practice and research should be reflected in the draft guidance. Other systematic reviews have also concluded probiotic use is associated with a significant reduction in the risk of developing CDAD in patients receiving antibiotics - Lau, C.S. and Chamberlain, R.S., 2016. Probiotics are effective at preventing Clostridium difficile-associated diarrhea: a systematic review and meta-analysis. International journal of general medicine, 9, p.27.	seen in a UK population, which is about 3%, as advised by the committee expert witness. The authors of the Goldenberg et al 2017 review state that 'Trials with a baseline CDAD risk of 0% to 2% and 3% to 5% did not show any difference in risk but trials enrolling participants with a baseline risk of >5% for developing CDAD demonstrated a large 70% risk reduction (interaction P value = 0.01). This is detailed in the committee rationale in the guideline. Please note that the only UK study in the Goldenberg et al. 2017 Cochrane review (with a UK baseline risk factor for *C. difficile* infection) showed no effect from the intervention. NICE does not include study author conclusions or their implications for practice in guidelines. It is the role of the guideline committee to review the available evidence and make recommendations for practice. The Lau et al. 2016 systematic review was not included in the guideline (see appendix E of the evidence review) as it was of lower quality than the included Cochrane systematic review by Goldenberg et al. 2017.
39	Faculty of Homeopathy	Guideline	20	3	Consideration should be made to problems in using a meta-analysis approach to evaluating probiotics, and thereby due weight given to	The committee agreed that there is some evidence (with many limitations) of a small effect with probiotics in preventing *C.*

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					single studies also. To support my argument I have provided extracts from a technical book: 'Probiotics and Health Claims' Edited by Wolfgang Kneifel and Seppo Salminen. © 2011 Blackwell Publishing Ltd. ISBN: 978-1405194914 Chapter 3, p.46 In this respect, the combination of a probiotic strain with other strains or other functional ingredients particularly deserves attention. It is often assumed, and without any justification, that when combining probiotic strains their properties will simply 'add up.' It is unrealistic to assume that by combining, for example, an anti-inflammatory strain with a proinflammatory strain, both properties would remain present without influencing each other. Similar interaction can of course be expected for combinations with other active ingredients as well. Combining strains and predicting the functionality based on the properties of the components is challenging. Likewise, one cannot extract the properties for one strain from a tested combination of strains. Chap 4, p.64 4.5.1 Future therapeutic strategies: combination of strains? The mechanisms underlying the beneficial effects of probiotics are not completely understood, but numerous bacterial strains exhibit health benefit properties and they may differ markedly in their mode of action. Specific strains of probiotics have been shown to modulate the human gut microbiota,	*difficile* infection. However, because of concerns about the evidence base they could not identify any scenario when the use of probiotics could be recommended in people taking antibiotics. Following stakeholder consultation, the recommendation has been amended so that it focuses on the advice given to people and states 'Do not advise people taking antibiotics to take prebiotics or probiotics to prevent *C. difficile* infection'. Please note that the Goldenberg et al. 2017 Cochrane review includes an *a priori* subgroup analyses on probiotic species, which found that 'the criteria supporting a species specific effect are mixed and we are unable to clearly identify a credible subgroup effect'.

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					inhibit colonization of pathogens or modulate the immune system but no single strain possesses all properties. The selective combination of strains could be a valuable approach by providing several microbial characteristics not exhibited by a single strain. This approach could be especially efficient in the treatment of gastrointestinal diseases, which are generally very complex and which comprise a high number of different syndromes and symptoms such as IBD and IBS. Studies on different pathologies have demonstrated that the administration of multiple probiotic organisms might expand their capacity for immunological modulation. Chap 11, p.162 – 164 11.9 is a meta-analytical approach appropriate for assessing the efficacy of probiotics? Analysis of the results of published meta-analyses reveals that probiotics administered for treatment of a specific disease or condition are all evaluated together. Is it appropriate to pool data on different probiotic microorganisms? It is tempting for reviewers to produce a single estimate of the treatment effect (presented as a diamond at the bottom of a forest plot). However, the results of a meta-analysis of all probiotics, regardless of the microorganisms used, may be misleading if appropriate consideration is not given to interpretation of the pooled results. Below, some arguments for and against the pooling	

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					of data on different probiotics, and some suggestions for solutions, are discussed. 11.9.1 Arguments for pooling data The value of performing a meta-analysis is that by combining trials, the sample size is increased and thus the power. Pooled data on different probiotics allow one to establish whether there is evidence of an effect, determine the direction of the effect, determine the size of the effect (and the 95% CI around the effect), assess the consistency of the effect across studies, and identify the most promising probiotic(s). If there are many trials involving the administration of different probiotics to different participants with similar results consistently being seen in the various trials, the effect of the probiotic(s) has some generalizability. In addition, pooled data on different probiotics are important for demonstrating whether further research on these probiotics is substantiated. If so, this pooled data potentially may help to identify the most promising microorganisms as well as the research questions to be addressed in future studies. 11.9.2 Arguments against pooling data There are a number of arguments against pooling data. First, there is evidence that the beneficial effects of probiotics, particularly the immunomodulatory effects of individual probiotics observed in the host, differ greatly and are strain specific. For example, it is demonstrated that treatment with B. infantis 35624, but not L. salivarius UCC4331, resulted in normalization of the ratio of an	

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					anti-inflammatory to a proinflammatory cytokine. Second, probiotics vary by organism. In addition to the most commonly used lactic acid bacteria (e.g. lactobacilli, bifidobacteria), the yeast S. boulardii is often used. All these probiotics have different properties and antipathogenic mechanisms. Consequently, their efficacy may vary. For example, limited evidence suggests that S. boulardii, but not lactobacilli, is effective in preventing recurrent Clostridium difficile associated diarrhea. Third, the dose of probiotics may be important, and studies have shown a greater dose of a particular probiotic having efficacy compared to a lower dose. Finally, the results of some studies do suggest a different response to probiotics in various populations, e.g. ethnic, regional, age groups, and settings (hospital versus community) are all variables. Thus, the results observed in one population or setting cannot be simply extrapolated to the other. Collectively, these data suggest that is hard to consider probiotic supplementation as a homogeneous intervention. Pooling data from different genera, species, strains, and doses of probiotics obtained in different populations, presumably with variations in their native intestinal microbiota, may result in misleading conclusions. The risk is that the results could be erroneously extrapolated to other probiotics or other patient groups, and that	

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					significant benefits in trials are neutralised out by the pooling of data. 11.10 What could be the solution? Given these concerns, the best approach would be to perform a meta-analysis evaluating the effect of administering a clearly defined, single-organism probiotic preparation or an equally well-defined combination of probiotic microorganisms for treatment of a specific disease or condition. However, a lack of data often makes this infeasible. With few exceptions, only seldom are there data from more than single studies on given probiotic microorganism(s). There are various factors that discourage simple repetition (duplication) of trials that could clarify the effect of a given probiotic. These factors include a lack of scientific novelty and/or a lack of interest by potential sponsors in cases involving the administration of a commercially available probiotic product that has been proven effective in a single study. Another approach could be, and often is, to perform a review of all probiotics and then to perform subgroup analyses based on factors considered a priori that could potentially influence the magnitude of the treatment response.	
40	Faculty of Homeopathy	Guideline	20	13	When considering the relatively low economic costs of including probiotics into a treatment protocol, we are concerned there may be a erroneous use of the rationale for making this decision against the routine use of probiotics. Granted there is more work to be done on	Thank you for your comment. The committee agreed that given they were not confident in the evidence base for the clinical effectiveness of probiotics, it would necessarily follow that they could also not be confident in the cost-effectiveness of

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					specific probiotic strains and protocols, but that could be part of a recommendation statement.	their use, since a robust cost-effectiveness analysis is dependent on reliable data on clinical effectiveness. The committee could not identify any scenario when the use of probiotics could be recommended in people taking antibiotics.
41	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	2	9	We often get tangled with definitions of relapse and recurrent infections. Would it be useful to define these as the guidance has done for severity of disease?	Thank you for your comment. These terms have been added to the 'Terms used in the guideline' section, and included below the prescribing table (table 1).
42	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	2	13-16	Should anti-motility agents and laxative be added under section 1.1.3	Thank you for your comment. The recommendation has been amended to include reviewing the need to continue treatment with other medicines with gastrointestinal activity or adverse effects, such as laxatives. This includes antimotility medicines.
43	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	3	16-18	Should laxatives be added for review?	Thank you for your comment. The recommendation has been amended to include reviewing the need to continue treatment with other medicines with gastrointestinal activity or adverse effects, such as laxatives.
44	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	5-6	Table 1	Table 1; Should we add beside vancomycin the word 'reconstituted' powder for solution?	Thank you for your comment. This has been added to the prescribing table (table 1).
45	UK Clinical Pharmacy Association	Guideline	5-6	Table 1	Should we clarify when antibiotic treatment is ineffective? Is this after a full course of treatment is completed or if the patient is still	Thank you for your comment. The committee agreed that resolution of diarrhoea may not happen by day 3 to 5.

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	(UKCPA) Infection Committee				experiencing loose stools at day 5 into therapy?	This has been clarified in the prescribing table (table 1) which states 'use clinical judgement to determine whether antibiotic treatment for C. difficile infection is ineffective. It is not usually possible to determine this until day 7 because diarrhoea may take 1 to 2 weeks to resolve'. The recommendation on reassessment has been amended to remove the 3 to 5 day time period.
46	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	5-6	Table 1	Should the term 'first recurrence' be added to the last line of the table? Would subsequent recurrences be referred to a specialist?	Thank you for your comment. The committee recognised that the choice of antibiotic for a recurrent infection may depend on a range of factors. The committee agreed it was appropriate for both vancomycin and fidaxomicin to be first-line options for further episodes, with the choice coming down to an individual patient decision based around severity, the risk of additional recurrences (which increases after each recurrent episode) and the time period between recurrences. The committee favoured fidaxomicin for more severe, more recent or multiple recurrent episodes, but felt vancomycin would be suitable for less severe or first recurrent episodes, or if there had been a long period of time between episodes. The prescribing table (table 1) has been amended to reflect this change. A recommendation has been added to ensure people in hospital with suspected or

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						confirmed *C. difficile* infection have care from of a multidisciplinary team.
47	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	5-6	Table 1	Should a comment be added to the table for 'life threatening' infection e.g. seek specialist advice?	Thank you for your comment. The prescribing table (table 1) states that urgent specialist advice should be sought for life-threatening *C. difficile* infection.
48	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	General		Guideline's reliance on "seek specialist advice" is unhelpful.	Thank you for your comment. Following stakeholder consultation, in addition to seeking specialist advice, a specialist option (agreed by committee consensus) has been added to the prescribing table for treating *C. difficile* infection. For an infection that has not responded to first- and second-line antibiotics, up to 500 mg oral vancomycin with or without intravenous metronidazole is included. For a life-threatening infection, high-dose (500 mg) oral vancomycin with intravenous metronidazole is included.
49	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	5-6	Table 1	RE: life-threatening infection – why has an empiric regimen not been given (even if the "seek advice" caveat is retained)? Not aware of any great controversy over Vancomycin 500mg QDS PO + Metronidazole 500mg TDS IV (as per IDSA).	Thank you for your comment. Following stakeholder consultation, in addition to seeking specialist advice, a specialist option (agreed by committee consensus) has been added to the prescribing table for treating *C. difficile* infection. For an infection that has not responded to first- and second-line antibiotics, up to 500 mg oral vancomycin with or without intravenous metronidazole is included. For a life-threatening infection, high-dose (500 mg) oral vancomycin with intravenous metronidazole is included.

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50	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	5-6	Table 1	Introduction of fidaxomicin as second line will have significant cost pressure. Will the cost implications be taken into account?	Thank you for your comment. The committee were aware of the higher cost of fidaxomicin compared to alternative antibiotics, and it was for this reason that cost-effectiveness modelling was prioritised for this topic. The results of that analysis were clear that fidaxomicin was the most cost-effective antibiotic to use as second-line treatment (primarily due to lower relapse rates meaning both improved clinical outcomes, and reduced costs for rehospitalisation). As well as the cost-effectiveness work undertaken, NICE will also be producing a resource impact tool alongside the guideline, which will estimate the additional costs associated with using fidaxomicin for this indication.
51	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	5-6	Table 1	Tapering vancomycin could be considered as a therapeutic option for recurrence. Whilst it is low quality evidence perhaps more cost effective.	Thank you for your comment. No evidence was identified comparing the use of tapering (or taper-pulse) vancomycin to standard antibiotics (evidence only compared it to FMT for people with a number of previous recurrences). The committee were aware that vancomycin is licensed to be given in a tapered or pulsed regimen and agreed this was one of a number of options that specialists could consider if standard antibiotic treatment was unsuccessful, but in the absence of evidence did not believe it was appropriate to include it in the recommendations.

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						The cost-effectiveness analysis used to compare different antibiotic treatment options for first- and second-line therapy assumed that third-line therapy would be a mixture of vancomycin taper-pulse and FMT, with fourth-line treatment being FMT.
52	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	5-6		No option for severe C diff. Could we not include oral vancomycin and IV metronidazole? Appreciate the evidence for this is not great but in practice these are the only options left and is recommended by IDSA.	Thank you for your comment. Following stakeholder consultation, in addition to seeking specialist advice, a specialist option (agreed by committee consensus) has been added to the prescribing table for treating *C. difficile* infection. For an infection that has not responded to first- and second-line antibiotics, up to 500 mg oral vancomycin with or without intravenous metronidazole is included. For a life-threatening infection, high-dose (500 mg) oral vancomycin with intravenous metronidazole is included.
53	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Visual Summary			On the visual summary page – under assessment in the left hand box it states assess severity of infection but doesn't refer to criteria to assess against or how this changes initial management?	Thank you for your comment. The visual summary is published in a consistent format for all NICE antimicrobial prescribing guidelines and includes a summary of all recommendations. This format has been very well received by users. Unfortunately, it was not possible to fit the suggested information into the visual summary due to the limited space available. This is included in the guideline and there are hyperlinks to the definitions from the relevant guideline recommendations.

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54	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	General		Unclear on what basis the 12 weeks to distinguish relapse <12 weeks and recurrence >12 weeks was based on	Thank you for your comment. Recurrence of *C. difficile* infection is as a further episode of *C. difficile* infection occurring after a previous episode. There is no agreement on the precise definition of relapse, which is more likely to be with the same *C. difficile* strain, or recurrence, which is more likely to be with a different *C. difficile* strain, and this cannot be distinguished clinically. In this guideline, the committee discussed and agreed by consensus that 12 weeks was a reasonable cut-off point between relapse (occurring within 12 weeks of previous symptom resolution) and recurrence (occurring more than 12 weeks after previous symptom resolution). This has been added to the 'Terms used in the guideline' section, and included below the prescribing table (table 1).
55	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	General		No guidance on escalation treatment if poor response to first or second line treatment in the visual summary treatment table- just states seek specialist advice	Thank you for your comment. Following stakeholder consultation, in addition to seeking specialist advice, a specialist option (agreed by committee consensus) has been added to the prescribing table for treating *C. difficile* infection. For an infection that has not responded to first- and second-line antibiotics, up to 500 mg oral vancomycin with or without intravenous metronidazole is included.
56	UK Clinical Pharmacy Association	Guideline	General		Lack of any guidance on severe disease, escalation to surgery etc.	Thank you for your comment. Following stakeholder consultation, in addition to seeking specialist advice, a specialist

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	(UKCPA) Infection Committee					option (agreed by committee consensus) has been added to the prescribing table for treating C. difficile infection. For an infection that has not responded to first and second line antibiotics, up to 500 mg oral vancomycin with or without intravenous metronidazole is included. For a life threatening infection, high-dose (500 mg) oral vancomycin with intravenous metronidazole is included. Surgical interventions are outside the scope of this guideline. However, a recommendation has been added to ensure people in hospital with suspected or confirmed *C. difficile* infection have care from of a multidisciplinary team that includes a surgeon, as needed.
57	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	General		No mention of gastroenterology specialist being involved in management in visual summary or full guideline (referral to microbiologist or infectious disease specialist only mentioned)	Thank you for your comment. The recommendation has been amended to include referral to a gastroenterologist. A recommendation has also been added to ensure people in hospital with suspected or confirmed *C. difficile* infection have care from a multidisciplinary team that includes a gastroenterologist, as needed.
58	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	4	1.1.11	Reassessment of response to treatment between 3-5 days- this is not clear that patients should be reassessed based on their severity of treatment- i.e. up to twice daily for severe/life threatening disease.	Thank you for your comment. The committee recognised that people in hospital with *C. difficile* infection would be reviewed on a regular basis, at least daily. For people in the community, reassessment would be needed if symptoms or signs do not improve as expected or worsen rapidly or significantly

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						at any time. The recommendation has been amended to reflect this, and the 3 to 5 day time period has been removed.
59	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	General		There is lots of discussion about dehydration and fluid management but no mention anywhere regarding nutrition. No mention of referral to dietician	Thank you for your comment. A recommendation has been added to ensure people in hospital with suspected or confirmed *C. difficile* infection have care from a multidisciplinary team that includes a dietitian, as needed.
60	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	11	11/12	This procedure (FMT) should only be considered for patients with recurrent *C. difficile* infections that have failed to respond to antibiotics and other treatments'. Unclear what they meant by other treatments they were referring to at this point.	Thank you for your comment. This wording in the rationale reflected wording in NICE's interventional procedure guidance on FMT for recurrent *C. difficile* infection but following stakeholder comment it has been removed for greater clarity.
61	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	General		Oral vancomycin and fidaxomicin can be difficult to get supplied in a timely manner via community pharmacies resulting in delays in initiation of treatment the guidance needs to highlight that treatment needs to be start that day and an arrangement for community emergency supply needs to be in place so there are not delays in intuition of *C. difficile* treatment.	Thank you for your comment. The committee recognised that there are some implementation challenges for this guideline. Local health organisations, health and social care practitioners and other stakeholders will need to work collaboratively to ensure that appropriate treatment is available in primary care for people with suspected or confirmed *C. difficile* infection. NICE are working with other national stakeholders such as NHS England and Improvement (including procurement teams) to support implementation of the guideline. The committee discussed whether they could give further information about when treatment should be started. As with all infections that require antibiotics, treatment

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						should be started as soon as possible. Following discussion, they agreed that for people in the community, prescribers should consider seeking prompt specialist advice from a microbiologist or infectious diseases specialist before starting treatment, and this has been added to the recommendation.
62	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	General		There is a lot of mention about seeking specialist advice in the draft, would it be possible to clarify which type of specialist? e.g. microbiology, gastro team, antimicrobial team/pharmacy	Thank you for your comment. This has been clarified throughout the recommendations. A recommendation has been added to ensure people in hospital with suspected or confirmed *C. difficile* infection have care from of a multidisciplinary team that includes a microbiologist or infectious diseases specialist, gastroenterologist, surgeon, pharmacist and dietitian, as needed.
63	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	General		Recommend Gastro review, micro review and antimicrobial pharmacy review should be sought where stubborn or recurring issues? This generally happens in hospital settings, but not sure GPs would think to do this.	Thank you for your comment. A recommendation has been added to ensure people in hospital with suspected or confirmed *C. difficile* infection have care from a multidisciplinary team that includes a microbiologist or infectious diseases specialist, gastroenterologist, surgeon, pharmacist and dietitian, as needed. There are also recommendations for people in the community to ensure they are referred to hospital as appropriate.
64	UK Clinical Pharmacy Association (UKCPA)	Guideline	General		Can you please add some recommendation for weekly antimicrobial and infection control follow up of GDH or C.diff for all in-patient cases? We do this (pre-covid we were, hoping to resume asap) even for patients that	Thank you for your comment. Infection control procedures and antimicrobial stewardship is outside the scope of this guideline. The guideline now signposts to other relevant national guidance in the

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	Infection Committee				were not C.diff/GDH on this admission, to avoid recurrence.	'Preventing *C. difficile* infection' section, which cover these aspects – Public Health England's guidance on *C. difficile* infection: how to deal with the problem, NICE's guidance on healthcare-associated infections and NICE's guidance on antimicrobial stewardship.
65	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	General		Can you please add recommendations and narrative around GDH testing and actions. Including GDH positive, toxin negative patients showing symptoms.	Thank you for your comment. Diagnosis of *C. difficile* infection is outside the scope of this guideline. Users are signposted to Public Health England's guidance on diagnosis and reporting.
66	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	General		Please add some information around stool charts, and other considerations to guide decisions as part of the day 3 review	Thank you for your comment. The committee recognised that people in hospital with *C. difficile* infection would be reviewed on a regular basis, at least daily. For people in the community, reassessment would be needed if symptoms or signs do not improve as expected or worsen rapidly or significantly at any time. The recommendation has been amended to reflect this, and the 3 to 5 day time period has been removed. Other than the actions related to antibiotic treatment, the committee was not able to give more specific details about the assessment or reassessment as this will depend on individual patient factors. Further information (for example on stool sample tests) is available in Public Health England's guidance on diagnosis and

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						reporting, and this is signposted in the recommendations on reassessment.
67	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	2	1.1.1	Please strengthen the bit around Day 3 review (rather than day 5) to ensure the treatment is actually working, rather than going to 5 days, then the 10 days straight. Can do day 3 and day 5, as sometimes the gut does seize up, giving a false impression on stool chart in regard to frequency? Every day counts	Thank you for your comment. The committee recognised that people in hospital with *C. difficile* infection would be reviewed on a regular basis, at least daily. For people in the community, reassessment would be needed if symptoms or signs do not improve as expected or worsen rapidly or significantly at any time. The recommendation has been amended to reflect this, and the 3 to 5 day time period has been removed.
68	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	2	1.1.2	Individual factors – to include medication please	Thank you for your comment. The committee agreed not to include concomitant medicines in individual factors, as review of medicines (such as any existing antibiotics) is covered in other recommendations.
69	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	2	1.1.3	Add review anti motility agent (mentioned in 1.1.9, but it would be worth reiterating it in 1.1.3 to provide a good summary for medications to review). Add review prokinetics, and to stop Laxatives (would seem obvious but not the case on ground level)	Thank you for your comment. The recommendation has been amended to include reviewing the need to continue treatment with other medicines with gastrointestinal activity or adverse effects, such as laxatives. This includes prokinetic medicines.
70	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	5	1.2	Please bring metronidazole back as an option on the table! We use this as first line with great results, despite many other Trust pulling back from it. We exclude the use of metronidazole suspension as the SPC used to have a line in it (way back) saying not to use it in diarrhoea or short gut syndromes as not sure gastric enzymes will have an	Thank you for your comment. The use of metronidazole was one of the options tested in the cost-effectiveness modelling used to underpin this guideline. When the costs of rehospitalisation were included in the analysis, the committee agreed the results were clear that vancomycin was a more cost-effective first-line treatment than

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					opportunity to activate the metronidazole in that formulation. Please bring it back. Whilst other Trusts may have moved away from it amidst high C.diff numbers, we have actually been doing very well as had been managing with this drug, since pairing up with weekly C.diff ward rounds to follow up on all C.diff/GDH patients.	metronidazole, and that it was dominant in most scenarios (meaning the use of vancomycin is both less costly and more effective than the use of metronidazole). These results are based on the clinical evidence review, which showed that metronidazole has both lower initial cure rates and higher recurrence rates than vancomycin. Considering all this evidence, the committee concluded that it was appropriate to retain the recommendation for vancomycin to be the first-line antibiotic of choice.
71	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	General		Please add some dosing information on tapering courses for recurrent and relapsing C.diff cases. This is not needed often, but having worked at 4 different Trusts, the approach seems to be similar in principle.	Thank you for your comment. Tapering or pulsed regimens are not recommended in the guideline to treat recurrent infection due to the lack of evidence. In the evidence review, its use was limited to studies in which there was co-administration of faecal microbiota transplant. The committee were aware that vancomycin is licensed to be given in a tapered or pulsed regimen and agreed this was one of a number of options that specialists could consider if standard antibiotic treatment was unsuccessful, but in the absence of evidence did not believe it was appropriate to include it in the recommendations.
72	UK Clinical Pharmacy Association	Guideline	General		Where oral medicines are not an option at all, including no option for feeding tube, and patient not consenting to FMT, please bring	Thank you for your comment. The committee agreed that the scenario described was likely to be a rare

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	(UKCPA) Infection Committee				IV metronidazole as a recommendation for careful consideration. We know this is less likely to be effective compared to oral but do find this can still be a game changer for some cases. These situations do occur on care of the elderly/dementia wards.	occurrence. The use of metronidazole was one of the options tested in the cost-effectiveness modelling used to underpin this guideline. When the costs of rehospitalisation were included in the analysis, the committee agreed the results were clear that vancomycin was a more cost-effective first-line treatment than metronidazole, and that it was dominant in most scenarios (meaning the use of vancomycin is both less costly and more effective than the use of metronidazole). These results are based on the clinical evidence review, which showed that metronidazole has both lower initial cure rates and higher recurrence rates than vancomycin. Following stakeholder consultation, the committee agreed that for people who cannot take oral medicines, specialist advice should be sought from a gastroenterologist or pharmacist about alternative enteral routes for antibiotics. This has been added to the recommendation.
73	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	General		Some recommendation around management of sore skin due to excessive diarrhoea. Barrier creams are used. Sometimes prescribers go for flamazine cream where they consider this is along the lines of chemical burns from the toxin. Having some recommendation on this will help prescribers.	Thank you for your comment. This is outside the scope of this guideline.

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74	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	9	Lines 26/27	Would we refer to any other national guideline about recommended durations of PPI as many patients do not have PPs reviewed after this time. Also, when stopping PPI (where appropriate), a tapered stop may be better than a hard stop, to avoid rebound acid reflux?	Thank you for your comment. No evidence was identified from the literature search on the effect of stopping or de-escalating proton pump inhibitors. However, the committee recognised the importance of reviewing the need to continue any treatment with proton pump inhibitors, and this is included in the recommendations.
75	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	17	17-23	Supports request to have IV metronidazole on the table please	Thank you for your comment. Following stakeholder consultation, in addition to seeking specialist advice, a specialist option (agreed by committee consensus) has been added to the prescribing table for treating *C. difficile* infection. For an infection that has not responded to first- and second-line antibiotics, up to 500 mg oral vancomycin with or without intravenous metronidazole is included. For a life-threatening infection, high-dose (500 mg) oral vancomycin with intravenous metronidazole is included.
76	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	18	2-3	Supports request around section 1.2, re pulsed/tapered courses to be standardised a little, or at least mentioned in the main guideline	Thank you for your comment. No evidence was identified comparing the use of tapering (or taper-pulse) vancomycin to standard antibiotics (evidence only compared it to FMT for people with a number of previous recurrences). The committee were aware that vancomycin is licensed to be given in a tapered or pulsed regimen and agreed this was one of a number of options that specialists could consider if standard antibiotic treatment was unsuccessful, but in the absence of

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						evidence did not believe it was appropriate to include it in the recommendations.
77	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	General		I welcome the recommendation to use vancomycin as first line treatment for *C.difficile* infection however this recommendation brings significant challenges both in primary and secondary care, where a patient requires a liquid preparation. The only licensed preparations of vancomycin solution are powder for solution presented in glass vials that have dual route of administration (intravenous and oral). In primary care, patients and carers are unlikely have the skills to manipulate the vials to be able to administer this product. Due to unfamiliarity with the product in primary care, without clear information relating to how it should be prescribed in primary care, and information on how to dispense the product, there is a significant likelihood that patients will miss doses potentially causing harm. Where patients are unable to have second line fidaxomicin due to contraindications or unacceptable side effects, this issue has the potential to result in patients admitted to hospital unnecessarily. In 2007, following the National Patient Safety Agency (NPSA) issued several Patient Safety Alerts relating to the use injectable and liquid medicines. Under the 'National Patient Safety Agency Patient Safety Alert - Promoting safer measurement and administration of liquid medicines via oral and other enteral routes' (2007), organisations were directed to only	Thank you for your comment and support for the recommendation on first line antibiotic treatment. The committee recognised that there are some implementation challenges for this guideline. Local health organisations, health and social care practitioners and other stakeholders will need to work collaboratively to ensure that appropriate treatment is available for people with suspected or confirmed *C. difficile* infection. NICE are working with other national stakeholders such as NHS England and Improvement (including procurement teams) to support implementation of the guideline. From their experience, the committee agreed that the number of people treated in the community for *C. difficile* infection who are also unable to take oral medicines (vancomycin capsules) is likely to be extremely small. The committee recognised the potential for medication errors when vancomycin powder for solution is reconstituted for oral or enteral administration. They agreed that vancomycin capsules are the preferred formulation to give vancomycin orally. They were aware that vancomycin powder for

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					use labelled oral/enteral syringes that cannot be connected to intravenous catheters or ports to measure and administer oral liquid medicines. It is not possible to prepare licensed vancomycin powder for solution for oral using syringes that cannot be connected to intravenous catheters or port and therefore it is not possible comply with the NPSA alert. Under 'NPSA Patient Safety Alert - Promoting safer use of injectable medications in (2007)', the use of open systems to prepare injectable medicines is discouraged. An open system may be used as part of the reconstitution of vancomycin in order to reduce the use of syringes that can be connected to intravenous catheter ports but this introduces the risk of the administration of a product other than vancomycin to the patient. This has subsequently been reiterated by an NHS England Patient Safety Alert Stage One Warning - Risk of death or severe harm due to inadvertent injection of skin preparation solution (2015) and an NHS Improvement Patient Safety Alert in 2016 (Restricted use of open systems for injectable medication (2016). There is no UK licensed product of vancomycin that can be administered orally that is compatible with these important patient safety alerts. A risk assessment performed in an English hospital trust determined that using licensed vancomycin powder for solution that is also suitable for intravenous administration is not an acceptable practice due to the risk of incorrect route of	solution is also licensed to be given orally for *C. difficile* infection, and this is used in some settings (particularly if people cannot take solid oral medicines). However, they discussed that locally agreed protocols should be in place to reduce the risk of medication errors around reconstitution and administration, and to take account of the practicalities of administration, particularly in community settings. In response to stakeholder concerns, the committee have made the following changes to the recommendations: • Table 1 includes the oral dosage for vancomycin but no longer states the dosage form (capsules or reconstituted powder for solution given orally). • A recommendation was added that for people who cannot take oral medicines, specialist advice should be sought from a gastroenterologist or pharmacist about alternative enteral routes for antibiotics. The committee recognised that rarely, hospital admission may be required to ensure safe and appropriate administration.

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					administration. There is currently mixed practice across the country with respect to administering this product in hospitals; some extemporaneous dispensing, the use specials, the use of a FDA approved product (Firvanq) and the use of the vials at ward level is seen. The level of complexity across the system only adds to risk. I believe NICE have a responsibility to ensure NPSA alerts and Patient Safety Alerts can be implemented under NICE guidelines therefore improved information around the use of vancomycin in liquid form should be provided as part of the guidelines to assist GPs and hospitals in using the guideline while meeting these alerts. Without this additional information, the recommendation to use vancomycin first line is not likely to be successfully implemented in some patients requiring liquid preparations.	
78	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	5	14	In terms of paediatric treatment – agree need for specialist input – suggest re-word to: take account of licensed indications in this group / availability of suitable formulations. Please also note that metronidazole is still occasionally recommended for use in paediatrics particularly if outpatient treatment is necessary due to its availability as a ready to use suspension (appreciate can be issues with formulation & diarrhea / non acidic environment if children taking concurrent PPI therapy in which case we often advise to crush & disperse the tablets as these are not the benzoate form – which is still far easier	Thank you for your comment. The suggestion to include the availability of suitable formulations has been incorporated into the recommendation. The committee discussed the clinical effectiveness of metronidazole in children and young people. The use of metronidazole was one of the options tested in the cost-effectiveness modelling in adults used to underpin this guideline. When the costs of rehospitalisation were included in the analysis, the committee agreed the results were clear that

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					than families having to reconstitute vancomycin vials at home & withdraw a proportion of the vial – see comment above) – appreciate that metronidazole is no longer recommended as an option for adults & therefore is not listed in Table 1 however perhaps information re metronidazole specifically for use in paediatrics could be added to the Antibiotics for children section p18.	vancomycin was a more cost-effective first-line treatment than metronidazole, and that it was dominant in most scenarios (meaning the use of vancomycin is both less costly and more effective than the use of metronidazole). These results are based on the clinical evidence review in adults, which showed that metronidazole has both lower initial cure rates and higher recurrence rates than vancomycin. They agreed that no differences in clinical effectiveness would be expected in children and young people. Considering all this evidence, the committee concluded that it was appropriate to retain the recommendation for vancomycin to be the first-line antibiotic of choice in adults. They concluded that antibiotic choice in children and young people should be based on what is recommended in adults, taking into account licensed indications for children and young people, and what products are available.
79	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	3		Role for supportive nutrition ?oral supplements under dietetic direction ?NG feeding rather than use of IV fluids alone	Thank you for your comment. This is outside the scope of this guideline. However, a recommendation has been added to ensure people in hospital with suspected or confirmed *C. difficile* infection have care from a multidisciplinary team that includes a dietitian, as needed.
80	UK Clinical Pharmacy	Guideline	4		Suggest at least daily review of in-patients rather than 3-5 days as recommended. Very	Thank you for your comment. The committee recognised that people in

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	Association (UKCPA) Infection Committee				flimsy if no guidance at all re need for regular review [and why] and tools used to assess condition [stool chart, fall in CRP, improvement in imaging]	hospital with *C. difficile* infection would be reviewed on a regular basis, at least daily. For people in the community, reassessment would be needed if symptoms or signs do not improve as expected or worsen rapidly or significantly at any time. The recommendation has been amended to reflect this, and the 3 to 5 day time period has been removed. Other than the actions related to antibiotic treatment, the committee was not able to give more specific details about the assessment or reassessment as this will depend on individual patient factors. Further information (for example on stool sample tests) is available in Public Health England's guidance on diagnosis and reporting, and this is signposted in the recommendations on reassessment.
81	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	5		Close collaborative working with duty gastroenterologist as well as duty microbiologist. Involvement of duty surgeon if signs of fulminant colitis in association with duty gastroenterologist	Thank you for your comment. A recommendation has been added to ensure people in hospital with suspected or confirmed *C. difficile* infection have care from a multidisciplinary team that includes a microbiologist or infectious diseases specialist, gastroenterologist, surgeon, pharmacist and dietitian, as needed.
82	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	5	Table 1	Recommend include rectal routes of vancomycin if PO route is not possible If vancomycin allergy – what alternative to use as treatment might be helpful	Thank you for your comment. Following stakeholder consultation, the committee agreed that for people who cannot take oral medicines, specialist advice should be sought from a gastroenterologist or pharmacist about alternative enteral routes

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						for antibiotics. This has been added to the recommendation. Alternatives in the event of vancomycin allergy are not given as this is likely to be a very rare occurrence, and individualised clinical judgement would be used. Users are directed to the BNF for more information on appropriate use and dosing in specific populations (for example, hepatic impairment, renal impairment, pregnancy and breastfeeding).
83	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	7		No use of CRP No use of colitis terminology to differentiate between diarrhoea mild illness and diarrhoea due to severe colitis. Albumin? Abdominal girth / change in abdominal distension? Would also like to see surgical approach ie STC and ileostomy rather than defunctioning ileostomy and no colectomy	Thank you for your comment. Diagnosis of *C. difficile* infection is outside the scope of this guideline. Users are signposted to Public Health England's guidance on diagnosis and reporting. Surgical interventions are outside the scope of this guideline. However, a recommendation has been added to ensure people in hospital with suspected or confirmed *C. difficile* infection have care from a multidisciplinary team that includes a surgeon, as needed.
84	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	18		Antibiotics in special cases - Pregnancy? Breastfeeding?	From their experience, the committee agreed that it was very uncommon for a woman who is pregnant or breastfeeding to present with *C. difficile* infection. Users are directed to the BNF for more information on appropriate use and dosing in specific populations (for example, hepatic impairment, renal impairment, pregnancy and breastfeeding). Information is also given on the use of vancomycin and

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						fidaxomicin in pregnancy in the 'Medicines safety' section of the guideline.
85	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	2	line 5-7	The two PHE guidelines referred to here were published in 2012 and 2008 respectively, whereas the more recent (albeit 2013) guideline on actual treatment of CDI is not referred to at all – is the intention that this guideline will replace the 2013 document?	Thank you for your comment. This guideline on *C. difficile* infection: antimicrobial prescribing is published jointly by NICE and Public Health England. It will update any Public Health England guidance recommendations on treating *C. difficile* infection. Other aspects of these guidelines will be retained, for example for recommendations on diagnosis and reporting. NICE will work closely with Public Health England to make sure this is clear for users.
86	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	3	Line 2	Define "young people" – what age does this go up to?	Thank you for your comment. NICE uses the following definitions: • children: up to 12 • young people: between 12 and 17 • adults: 18 and over. Children and young people 'under 18 years' has been added; please see NICE's style guide for more information.
87	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	3	Line 6	No mention of IV route here & I later see that severe & life-threatening disease is being excluded from this guideline – it would be worth making that clear earlier in the document	Thank you for your comment. Treatment for people with severe or life-threatening *C. difficile* infection is included in the guideline. Following stakeholder consultation, in addition to seeking specialist advice, a specialist option (agreed by committee consensus) has been added to the prescribing table for treating *C. difficile* infection. For an infection that has not responded to first- and second-line antibiotics, up to 500 mg oral vancomycin with or without

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						intravenous metronidazole is included. For a life-threatening infection, high-dose (500 mg) oral vancomycin with intravenous metronidazole is included. The committee discussed the most appropriate route of administration of antibiotics for *C. difficile* infection. They agreed that the enteral route is best because sufficient concentrations within the intestinal lumen need to be reached. The committee concluded that it is preferable to give antibiotics via the oral route or, if this is not possible, enterally in some other way (such as a nasogastric or enteral feeding tube, or rectally). Following stakeholder consultation, they advised seeking specialist advice on administration from a gastroenterologist or pharmacist if the oral or another enteral route is not available.
88	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	3	Line 12	"episodes that have not responded to antibiotics" – so is FMT only indicated for CDI that's not responded at all rather than for multiply recurrent episodes that may have been successfully treated in the past?	Thank you for your comment. The committee agreed that the recommendation reflects the evidence for faecal microbiota transplant (FMT), although the recommendation wording has now been amended for greater clarity.
89	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	4	Line 4	Any link for information on preventing the spread of infection? Would be useful here	Thank you for your comment. Infection control procedures and antimicrobial stewardship is outside the scope of this guideline. The guideline now signposts to other relevant national guidance in the 'Preventing *C. difficile* infection' section, which cover these aspects – Public Health

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						England's guidance on *C. difficile* infection: how to deal with the problem, NICE's guidance on healthcare-associated infections and NICE's guidance on antimicrobial stewardship.
90	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	5	Line 3	By severe symptoms here are we referring to T>38.5C or abdominal signs of severe colitis (as per definition of severe CDI) or are there other factors that community providers should be considering?	Thank you for your comment. The recommendation has been amended and no longer refers to 'severe symptoms'. The committee agreed that people in the community with suspected or confirmed *C. difficile* infection should be referred to hospital if they are severely unwell, or their symptoms or signs worsen rapidly or significantly at any time. The recommendation also states that people with a life-threatening infection should be referred urgently to hospital.
91	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	5	Line 8	Aren't all cases of CDI in hospital managed in conjunction with Micro/ID as a matter of course?	Thank you for your comment. A recommendation has been added to ensure people in hospital with suspected or confirmed *C. difficile* infection have care from a multidisciplinary team that includes a microbiologist or infectious diseases specialist, gastroenterologist, surgeon, pharmacist and dietitian, as needed.
92	UK Clinical Pharmacy Association (UKCPA) Infection Committee	Guideline	General		As you might expect, I've significant issues with the choice of ABx table, as this effectively relegates fidaxomicin to vanc-failure or relapse/recurrence, which is not where we use the drug & also not where we believe it's major efficacy lies. There is no option for using FDX for managing a first episode in patients at high risk of recurrence,	Thank you for your comment. We agree that the evidence supports fidaxomicin as the most clinically effective antibiotic choice (because of the lower risk of recurrence). However, NICE guidelines are required to take account of cost-effectiveness (not simply costs) in addition

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					which means that any organisation choosing to do so will need to fund that treatment itself or comply with this NICE guidance. The network analysis (the only source quoted for the antibiotic choice) states "Among the treatments for non-multiply recurrent infections by C difficile, the highest quality evidence indicates that fidaxomicin provides a sustained symptomatic cure most frequently. Fidaxomicin is a better treatment option than vancomycin for all patients except those with severe infections with C difficile and could be considered as a first-line therapy. Metronidazole should not be recommended for treatment of C difficile." Yet the choice of antibiotic for the guideline is vancomycin alone. Cost is clearly being prioritised over clinical efficacy. Also the evidence summary quotes Hvas et al (P22, line 21-24) as their evidence that fidaxomicin is not more effective than vancomycin in reducing recurrence: There were no statistically significant differences in clinical effectiveness (recurrence of *C. difficile* infection, clinical resolution of *C. difficile* infection, relapse of *C. difficile* infection at 5 weeks and adverse events) for oral vancomycin compared with fidaxomicin (Hvas et al. 2019). Yet that paper was not designed to answer that question – it was an investigation of FMT v fidaxomicin for treatment of recurrent CDI; in fact both FDX & VAN groups had already had a median of 4 prior CDI episodes before this study. However, the paper does show	to clinical effectiveness when making recommendations. A cost-effectiveness analysis was undertaken that compared various first- and second-line antibiotic choices, and vancomycin consistently emerged as the most cost-effective option. This remained true in higher risk populations, and when various additional scenarios were tested after stakeholder consultation, including adding additional mortality benefits with fidaxomicin. The committee were aware of various real-world evaluations of fidaxomicin but were confident that the RCTs (and network meta-analyses of these trials) provided the best estimates of comparative effectiveness to be used in the economic evaluation, and that this approach was consistent with that recommended in Developing NICE guidelines: the manual. The committee agreed that in principle there may exist a small group of patients who are at such high risk of recurrence at first presentation that the use of fidaxomicin could be justified, but noted no evidence was found on how this group could be identified, nor were there studies conducted in or that identified such a population. They therefore agreed the evidence supported the use of vancomycin as the standard first-line treatment for an initial episode of *C. difficile* infection.

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					that, numerically, fidaxomicin is superior to vancomycin (clinical resolution in 42% [10/24] for FDX v 19% [3/16] for VAN) – but this is relatively meaningless as the numbers involved were so low. A more suitable paper to quote looking at clinical efficacy in reducing risk of recurrence in first episode CDI would be Louie et al NEJM 2011 which showed significantly lower recurrence rates in FDx-treated patients than VAN-treated (13.3% v 24.0%, p=0.004). However, this was excluded because it was "duplicate: study considered in an included SR" (P211 of evidence summary). The existing & still valid NICE evidence summary on fidaxomicin also states "These studies suggest an advantage of fidaxomicin over vancomycin in preventing recurrence of CDI"…"in patients with CDI who need to continue on other antibiotics…fidaxomicin could be considered in such cases". The evidence summary quotes the network meta-analysis as the main evidence source for antibiotic choices, which ranks FDX as the highest ranked agent readily available within the UK, superior to both VAN & MTZ for attaining sustained symptomatic cure (P25 of evidence summary). FDX is also the highest ranking agent in the sub-group analysis carried out (P26 of evidence summary) The evidence summary only quotes evidence from 2 RCTs when looking at treatment of first recurrence of CDI, but it does not quote data from Cornely et al CID 2012 which compared FDX with VAN as part of the pivotal RCTs for	

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					FDX & which showed that FDX was equivalent to VAN in treating first recurrence of CDI but superior in preventing a 2nd recurrence (it notes in the reference review that this was also excluded because it was "duplicate: study considered in an included SR" (P200 of evidence summary). The economic model (Appendix M) is exceptionally thorough (& lengthy) but it's worth noting that the analysis did not include the real-world evaluation that was carried out on FDX, so was based on a set of arbitrary assumptions (their words) around risk ratios, recurrence rates & baseline efficacy rates, which significantly reduces its validity. So, general conclusions – I think that the restriction on FDX usage is too draconian; I don't think that the evidence that they chosen to make this decision is necessarily the most appropriate choice & I think that it will penalise organisations like ours who've used FDX successfully & have brought down CDI rates in our population to best-in-class levels. Should we have to comply with this guidance, I've no doubt that our CDI levels will increase & this guidance will be responsible.	

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93	North Central London CCG	Guideline	General	General	Could clarity be provided on the powder for solution preparation of vancomycin to be given orally? Is this the powder for solution for infusion or would this be an unlicensed 'specials' formulation? There are significant cost implications when using the unlicensed specials preparation.	Thank you for your comment. This is vancomycin reconstituted powder for solution given orally or by another enteral route, which is licensed for treating C. difficile infection. However, in response to stakeholder concerns, the committee have made the following changes to the recommendations: • Table 1 includes the oral dosage for vancomycin but no longer states the dosage form (capsules or reconstituted powder for solution given orally). • A recommendation was added that for people who cannot take oral medicines, specialist advice should be sought from a gastroenterologist or pharmacist about alternative enteral routes for antibiotics. NICE are working with other national stakeholders such as NHS England and Improvement (including procurement teams) to support implementation of the guideline.
94	North Central London CCG	Evidence review	General	General	Is there any comparative data on the cure and relapse rates for vancomycin and fidaxomycin? This would be helpful to calculate cost implications for the antibiotic choices for 2nd line and relapse treatment. Appreciate that the economic model is not yet published.	Thank you for your comment. The evidence review published alongside the guideline should provide the estimates you are looking for. As an example, tables 54 and 55 in the review provide odds ratios for the initial cure and relapse rates for vancomycin compared to fidaxomicin (and other antibiotic choices).

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						As well as the cost-effectiveness work undertaken, NICE will also be producing a resource impact tool alongside the guideline, which will estimate the additional costs associated with using fidaxomicin for this indication.
95	North Central London CCG	Guideline	18	19	If there is no statistical difference between fidaxomycin and vancomycin in those patients under 18 years (especially those under 2 years) would vancomycin be the preferred choice antibiotic as fidaxomycin granules (unlicensedl) is a cost pressure? Could clarity be provided on the preferred antibiotic choice for paediatric patients?	Thank you for your comment. The committee discussed the treatment of *C. difficile* infection in children and young people at length. As this is very rare, they did not want to include a prescribing table for children and young people. Considering all the evidence, the committee concluded that it was reasonable to extrapolate the clinical evidence on antibiotic choice in adults to children and young people. They agreed that the choice of antibiotic in children and young people should be based on what is recommended in adults, taking into account what products are available, as well as the licensed indications for children and young people. This has now been reflected in the recommendation.
96	Scottish Antimicrobial Prescribing Group, Healthcare Improvement Scotland	Guidelines	General		Assessment of severity is recommended but then initial treatment is the same for all patients. This is contrary to Scottish guidance from HPS which advises on antibiotic choice based on severity markers. If severity is not being taken account of in choosing treatment (except life-threatening) then what is the purpose of stressing this.	Thank you for your comment. The committee agreed that the main reason to assess severity was to identify the appropriate place of care and overall management. The committee agreed that the recommendation should include an assessment of whether the current infection was a first or further- (recurrent)

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						episode. This was because it was a driver in the economic model and determines the antibiotic choice. The economic model did look at populations at increased and decreased risk of recurrence (which is not the same as severity but may capture some of the same individuals) and consistently found vancomycin to be a more cost-effective first-line treatment than fidaxomicin, even in people at higher risk of recurrence. Following stakeholder consultation, in addition to seeking specialist advice, high-dose (500 mg) oral vancomycin with intravenous metronidazole has been added to the prescribing table (agreed by committee consensus) as a specialist option for treating a life-threatening infection. This also supports the need to assess the severity of infection.
97	Scottish Antimicrobial Prescribing Group, Healthcare Improvement Scotland	Guidelines	Section 1.2		The use of vancomycin first line is contrary to practice in Scotland, which is to use metronidazole first line in mild-moderate cases and vancomycin first line in severe cases. We note that vancomycin has been deemed as most cost-effective and that metronidazole a less effective treatment. However, colleagues in Scotland have not identified treatment failure when using metronidazole as an issue. Currently CDI rates are stable in Scotland and acknowledge epidemiology may differ from that in England.	Thank you for your comment. The use of metronidazole was one of the options tested in the cost-effectiveness modelling used to underpin this guideline. When the costs of rehospitalisation were included in the analysis, the committee agreed the results were clear that vancomycin was a more cost-effective first-line treatment than metronidazole, and that it was dominant in most scenarios (meaning the use of vancomycin is both less costly and more effective than the use of metronidazole).

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					Using vancomycin first line presents several issues: increased cost, potential for increased VRE, no licensed oral liquid preparation (particularly problematic for community treatment) and use of licensed vials is not ideal.	These results are based on the clinical evidence review, which showed that metronidazole has both lower initial cure rates and higher recurrence rates than vancomycin. Considering all this evidence, the committee agreed it was appropriate to retain the recommendation for vancomycin to be the first-line antibiotic of choice.
8	Scottish Antimicrobial Prescribing Group, Healthcare Improvement Scotland	Key questions			*1.* ***Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why.*** As previously noted increased material cost of treatment and use of liquid preparation of vancomycin in the community. *2.* ***What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.)*** Availability of a licensed oral liquid formulation of vancomycin. 3. ***For the guideline:*** ***- Are there any recommendations that will be a significant change to practice or will be difficult to implement? If so, please give reasons why.*** Change to first line antibiotic choice and need for local guideline revision and awareness raising around change. ***- What are the key issues or learning points for professional groups?***	Thank you for your comment. NICE are working with other national stakeholders such as NHS England and Improvement (including procurement teams) to support implementation of the guideline, and your responses will help to inform that work.

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					Engagement and communication with health and care staff across hospital and community settings.	
99	Hywel Dda University Health Board	Guideline	2	15	Add review laxatives and prokinetics to the list with antibiotics and proton pump inhibitors	Thank you for your comment. The recommendation has been amended to include reviewing the need to continue treatment with other medicines with gastrointestinal activity or adverse effects, such as laxatives. This includes prokinetic medicines.
100	Hywel Dda University Health Board	Guideline	General	General	May be difficult in our rural location for patients to obtain vancomycin and fidaxomicin from community pharmacies as they don't tend to stock due to high costs. Distance between pharmacies and hospitals can be significant. This could lead to a delay in treatment.	Thank you for your comment. From their experience, the committee agreed that it was uncommon for people to present in the community with *C. difficile* infection, with GP committee members seeing very few cases. The committee recognised that there are some implementation challenges for this guideline. Local health organisations, health and social care practitioners and other stakeholders will need to work collaboratively to ensure that appropriate treatment is available in primary care for people with suspected or confirmed *C. difficile* infection. Timely access to treatment in rural locations is an important consideration that is not specific to treating *C. difficile infection*. However, this has now been included in the Equality impact assessment. NICE are working with other national stakeholders such as NHS England and Improvement (including

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						procurement teams) to support implementation of the guideline.
101	Hywel Dda University Health Board	Guideline	General	General	GPs unfamiliar with these agents and high cost may lead to non-adherence to the guidance in some areas. Information sessions and education will need to be an important consideration when rolling out this guidance	Thank you for your comment. From their experience, the committee agreed that it was uncommon for people to present in the community with *C. difficile* infection, with GP committee members seeing very few cases. They recognised the importance of additional support for primary care prescribers who may be unfamiliar with the recommended antibiotics. Following discussion, they agreed that for people in the community, prescribers should consider seeking prompt specialist advice from a microbiologist or infectious diseases specialist before starting treatment, and this has been added to the recommendation. The committee recognised that there are some implementation challenges for this guideline. Local health organisations, health and social care practitioners and other stakeholders will need to work collaboratively to ensure that appropriate treatment is available in primary care for people with suspected or confirmed *C. difficile* infection. NICE are working with other national stakeholders such as NHS England and Improvement (including procurement teams) to support implementation of the guideline.
102	Public Health England (PHE)	Guideline	18	19-21	*Clostridioides Difficile (C.diff*)-associated diarrhoea has not caused as much of a	Thank you for your comment. The study by McFarland et al. (2016) was identified in

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					clinical concern in children compared to adults[1]. In the absence of a need of escalation of therapy, please justify the change in recommendations from oral Vancomycin for children. [1] McFarland, L. V., Ozen, M., Dinleyici, E. C., & Goh, S. (2016). Comparison of pediatric and adult antibiotic-associated diarrhea and Clostridium difficile infections. *World journal of gastroenterology*, *22*(11), 3078–3104. https://doi.org/10.3748/wjg.v22.i11.3078	the literature search but is not an eligible study type (not a randomised controlled trial or systematic review). See appendix K in the evidence review. The committee discussed the clinical effectiveness of metronidazole in children and young people. The use of metronidazole was one of the options tested in the cost-effectiveness modelling in adults used to underpin this guideline. When the costs of rehospitalisation were included in the analysis, the committee agreed the results were clear that vancomycin was a more cost-effective first-line treatment than metronidazole, and that it was dominant in most scenarios (meaning the use of vancomycin is both less costly and more effective than the use of metronidazole). These results are based on the clinical evidence review in adults, which showed that metronidazole has both lower initial cure rates and higher recurrence rates than vancomycin. They agreed that no differences in clinical effectiveness would be expected in children and young people. They noted there may be some minor changes around cost-effectiveness in children (for example, the cost of an individual hospitalisation may be higher in children than in adults) but there was no evidence they would lead

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						to a substantive difference in the conclusions of the analysis, Considering all this evidence, the committee concluded that it was appropriate to retain the recommendation for vancomycin to be the first-line antibiotic of choice in adults. They concluded that antibiotic choice in children and young people should be based on what is recommended in adults, taking into account licensed indications for children and young people, and what products are available.
103	Public Health England (PHE)	Guideline	6	3-8 (section 1.3)	Although the guidance focuses on antimicrobial prescribing, it is recommended that further information is provided on how to prevent C. difficile, including signposting to other relevant information, such as the most recent guidance from the Health Protection Agency and Department of Health & Social Care on *Clostridium difficile* infection[2]. Health Protection Agency, Department of Health, Clostridium difficile infection: How to deal with the problem [Online]. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/340851/Clostridium_difficile_infection_how_to_deal_with_the_problem.pdf	Thank you for your comment. Infection control procedures and antimicrobial stewardship is outside the scope of this guideline. The guideline now signposts to other relevant national guidance in the 'Preventing *C. difficile* infection' section, which cover these aspects – Public Health England's guidance on *C. difficile* infection: how to deal with the problem, NICE's guidance on healthcare-associated infections and NICE's guidance on antimicrobial stewardship.
104	Tillotts Pharma UK Ltd	Guideline	General	General	We believe fidaxomicin should be recommended earlier in the treatment algorithm. NICE recognises the clinical effectiveness of fidaxomicin in the treatment of first and recurrent episodes of CDI.	Thank you for your comments. Your individual suggestions have been responded to in the comments where they appear. The committee have considered a number of additional scenarios after

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					We have reviewed the NICE economic model and identified two key parameters (mortality associated with recurrent infection is not included in the model and hospitalisation costs which are the lowest available in a range of published data) which significantly impact the overall cost effectiveness of fidaxomicin. If these parameters are amended in the model, fidaxomicin could become a cost effective (dominant) option, particularly in patients at increased risk. We therefore request that NICE considers these parameters in the model and updates the recommendations accordingly.	consultation, which are presented in appendix N of the evidence review and are explained in response to each of your comments they are relevant to. In particular, corrections were made to the cost of hospitalisation for recurrence, and a number of additional exploratory analysis were undertaken around difference possible mortality risks associated with recurrence. Having considered all this additional evidence, the committee remained of the opinion that the evidence supported vancomycin as the most cost-effective first-line option, and therefore this has been retained in the final recommendations.
105	Tillotts Pharma UK Ltd	Guideline	5	19	We believe that there are grounds in Table 1 to introduce fidaxomicin as a first-line antibiotic for a first episode of C. difficile infection in patients that are at high risk of recurrence based on well-established parameters such as age, frailty and comorbidities. This is supported by RCTs which demonstrate that fidaxomicin is superior to vancomycin in the reduction of recurrence. Recurrent infection is more difficult to treat and is associated with increased mortality, hospitalisations, severe outcomes, and higher costs than initial episodes (NICE: Evidence summary [ES13], Olsen et al 2015). It also inevitably increases the risk of C. difficile	Thank you for your comment. In the cost-effectiveness analysis that was undertaken comparing various first- and second-line antibiotic choices, vancomycin consistently emerged as the most cost-effective option. This remained true in higher risk populations, and when various additional scenarios were tested after stakeholder consultation, including adding additional mortality benefits with fidaxomicin (these additional analyses are presented in appendix N of the evidence review). The committee agreed that in principle there may exist a small group of patients who are at such high risk of recurrence at first presentation that the use of fidaxomicin could be justified, but noted no evidence

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					transmission (Eyre 2012), raising the likelihood of more patients being affected. For example, "First-line antibiotic for a first episode C. difficile infection in those patients at increased risk of recurrence, morbidity or mortality. Fidaxomicin: 200 mg orally twice a day for 10 days" **References** Eyre et al. Predictors of First Recurrence of Clostridium difficile Infection: Implications for Initial Management. Clinical Infectious Diseases 2012;55(S2):S77–87 NICE: Evidence summary [ES13] Preventing recurrence of Clostridium difficile infection: bezlotoxumab. 2017 Olsen MA et al. Recurrent Clostridium difficile infection is associated with increased mortality. Clin Microbiol Infect. 2015; 21: 164–170	was found on how this group could be identified, nor were there studies conducted in or that identified such a population. They therefore agreed the evidence supported the use of vancomycin as the standard first-line treatment for an initial episode of C difficile infection. The study by Olsen et al. 2015 is not an eligible study type (not a randomised controlled trial or systematic review). When discussing the economic modelling, the committee noted that the Olsen et al. study was based on data from 2003-2009 in the USA, and it is not clear they can be appropriately extrapolated to the current UK population. Nevertheless, the study by Olsen was used in some exploratory sensitivity analyses around mortality, and the committee remained confident the additional results generated did not impact on their conclusions. The committee also heard expert testimony about the relevance of these data to UK practice; see appendix N and O of the evidence review. The study by Eyre et al. 2012 is not an eligible study type (not a randomised controlled trial or systematic review).
106	Tillotts Pharma UK Ltd	Guideline	5	19	On the final row of Table 1 (recurrence) we request that the condition of "for severe infection" is removed from the fidaxomicin entry. We feel this limits the choice for the prescriber and there is no evidence for this	Thank you for your comment. The committee recognised that the choice of antibiotic for a recurrent infection may depend on a range of factors. The committee agreed it was appropriate for

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					restriction. The prescriber needs to consider the age, frailty and vulnerability of the patient suffering a recurrence of CDI.	both vancomycin and fidaxomicin to be first-line options for recurrent episodes, with the choice coming down to an individual patient decision based around severity, the risk of additional recurrences (which increases after each recurrent episode) and the time period between recurrences. The committee favoured fidaxomicin for more severe, more recent or multiple recurrent episodes, but felt vancomycin would be suitable for less severe or first recurrent episodes, or if there had been a long period of time between episodes. The prescribing table (table 1) has been amended to reflect this change.
107	Tillotts Pharma UK Ltd	Guideline	14	14	We are very concerned that the available real world evidence for fidaxomicin was excluded from consideration. These data confirm the findings of the clinical studies in which the safety and efficacy of fidaxomicin were confirmed, both in the treatment of initial infection and reduction of disease recurrence. They also provide confidence to health professionals that the clinical data are reproducible in an NHS setting and the benefits are genuinely achievable. Real word evidence presented by Goldenberg et al 2016 effectively demonstrates that fidaxomicin used first line has an impact on patient outcomes, with a meaningful improvement in rates of recurrence and all cause mortality compared to treatment prior to fidaxomicin.	Thank you for your comment. The committee agreed that various published evaluations back up the effectiveness of fidaxomicin as a treatment, in line with the findings from the randomised controlled trials included in the evidence review. They note, however, that it is those randomised trials that provide the best and most unbiased estimates of comparative treatment effectiveness, and therefore the estimates from those RCTs are the most appropriate ones to use to inform the cost-effectiveness modelling undertaken for this guideline. The study by Goldberg et al. 2016 is not an eligible study type (not a randomised controlled trial or systematic review).

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					In addition, Biswas et al 2015 demonstrated a significant reduction in the likelihood of patients treated with fidaxomicin contaminating their environment with C diff compared to those treated with either metronidazole or vancomycin. These findings add considerable weight to the argument that fidaxomicin could be considered a first line treatment option, particularly in those at risk of recurrence. **References** Biswas JS et al. Reduction in Clostridium difficile environmental contamination by hospitalized patients treated with fidaxomicin. Journal of Hospital Infection. 2015; 90: 267-270 Goldenberg SD et al. The impact of the introduction of fidaxomicin on the management of Clostridium difficile infection in seven NHS secondary care hospitals in England: a series of local service evaluations. Eur J Clin Microbiol Infect Dis. 2016; 35: 251–259	The study by Biswas et al. 2015 is not an eligible study type (not a randomised controlled trial or systematic review).
108	Tillotts Pharma UK Ltd	Guideline	14	21	We are unclear on the meaning of the committee's statement that use of fidaxomicin first line would incur unreasonably large opportunity costs. Use of less effective treatments, such as vancomycin, create their own opportunity costs that are not explored nor explained in the guideline or evidence review. Data suggests that use of vancomycin has a greater opportunity cost than fidaxomicin	Thank you for your comment. We disagree that the opportunity costs of vancomycin are not considered in the guideline – both the costs and QALY losses associated with higher recurrence rates compared to fidaxomicin are considered in the economic analysis undertaken. When the benefits and costs of both options are compared, vancomycin was found to be more cost-effective than fidaxomicin as a first-line treatment, and therefore the committee

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					when relapse, recurrence and cross infection are taken into consideration.	agreed it was appropriate to retain this in the recommendations.
109	Tillotts Pharma UK Ltd	Guideline	15	20	We welcome and agree with the committee's statement that there is a population of people in whom the risk of recurrence is likely to be greater than 30% ("increased risk" group, see Comment 2). This fact supports the view that fidaxomicin should be considered as a first line treatment in those patients, in order to reduce significantly the risk of relapse and the associated healthcare costs.	Thank you for your comment. It is important to note that the comment you refer to is in the context of people who are already suffering a recurrent infection. Specifically, it states 'The committee noted that the risk of future recurrence needed to be around 30% to 40% for fidaxomicin to be cost effective as a first-line option compared with vancomycin (at £30,000 per QALY gained). While they did not believe that this would be the case for all people with a recurrent infection, they did agree that there would be people with a risk of recurrence that high. They therefore agreed that it was appropriate for both vancomycin and fidaxomicin to be first-line options for further episodes, with the choice coming down to an individual patient decision based around severity, the risk of additional recurrences (which increases after each recurrent episode) and the time period between recurrences. The committee agreed therefore that this supports the position of fidaxomicin as an option to use first-line in recurrent infections (as is stated in the guideline), but should not be extrapolated to people with an initial infection. Considering initial infections, the committee agreed that in principle there may exist a small group of patients who are at such high risk of

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						recurrence at first presentation that the use of fidaxomicin could be justified, but noted no evidence was found on how this group could be identified, nor were there studies conducted in or that identified such a population. They therefore agreed the evidence supported the use of vancomycin as the standard first-line treatment for an initial episode of *C. difficile* infection. Should trials be published in future focusing specifically on an identified high-risk population and demonstrating additional benefits of fidaxomicin in this population, this could of course be considered in future updates of the guideline.
110	Tillotts Pharma UK Ltd	Guideline	22	1	We are concerned that, despite the profound improvement in sustained symptomatic cure rate for fidaxomicin compared to vancomycin presented by Beinortas et al 2018, fidaxomicin is omitted from the first line treatment options in the guideline, even in those patients at risk of recurrence. Beinortas performed sub-group analysis in which fidaxomicin continued to be highest ranked, further supporting this view. The evidence that fidaxomicin is more effective than vancomycin in achieving symptomatic cure is further supported in a Cochrane review conducted by Nelson et al in 2017. **References** Beinortas T et al. Comparative efficacy of treatments for Clostridium difficile infection: a	Thank you for your comment. The committee agreed there was evidence for higher rates of sustained symptomatic cure with fidaxomicin, driven by lower rates of recurrence with fidaxomicin compared to vancomycin. These data were all included as inputs to the cost-effectiveness modelling undertaken, in which vancomycin was found to be more cost-effectiveness as a first-line option than vancomycin. This remained true in higher risk populations, and when various additional scenarios were tested after stakeholder consultation, including adding additional mortality benefits with fidaxomicin.

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					systematic review and network meta-analysis. Lancet Infect Dis 2018; 18: 1035–44 Nelson RL et al. Antibiotic treatment for Clostridium difficile-associated diarrhoea in adults (Review). Cochrane Database of Systematic Reviews. 2017; Issue 3. Art. No.: CD004610	
111	Tillotts Pharma UK Ltd	Evidence review	37	1-50	We acknowledge and agree with the committee's comment that it is important to avoid over-prescribing of antibiotics in children unless infection is confirmed (page 10 lines 4-12). Data presented by Wolf et al 2019, arising from a trial in paediatric patients (148 patients <18 yrs, 30 of whom were <2yrs), provides evidence that both vancomycin and fidaxomicin are effective in treating CDI. In addition, fidaxomicin led to significantly better global cure rates (68.4%) compared to vancomycin (50.0%). The summary of this study by the committee on page 37 of the Evidence Summary reads "Fidaxomicin was not significantly different to vancomycin for global cure at the end of study (1 RCT, n=142, 68.4% versus 50.0%, RR 1.37, 95%CI 0.99 to 1.89, low quality evidence)." We are unclear why the committee state that this finding was not significant, contrary to the results in the original reference. These positive data were used in regulatory submissions and were the basis of approval for paediatric use in the fidaxomicin marketing authorisation.	Thank you for your comment. The statement 'Fidaxomicin was not significantly different to vancomycin for global cure at the end of study (1 RCT, n=142, 68.4% versus 50.0%, RR 1.37, 95%CI 0.99 to 1.89, low quality evidence),' was based on the lower end of the 95% CI crossing the line of no effect (1.00). The committee discussed the treatment of *C. difficile* infection in children and young people at length. As this is very rare, they did not want to include a prescribing table for children and young people. However, they concluded that antibiotic choice in children and young people should be based on what is recommended in adults, taking into account licensed indications for children and young people, and what products are available. Information about the fidaxomicin licence in children is given in the guideline rationale.

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					Fidaxomicin tablets are not licensed for use in children with a body weight under 12.5kg. Fidaxomicin granules for oral suspension preparation have a current UK marketing authorisation and will be made available in the UK without the need to import within 6 months of the publication of this guideline. The granules are licensed for use in adults and paediatric patients from birth. If required, a copy of the Summary of Product Characteristics can be seen on the MHRA website. Therefore, clearer guidance could be offered. **References** Wolf J et al. Safety and Efficacy of Fidaxomicin and Vancomycin in Children and Adolescents with Clostridioides (Clostridium) difficile Infection: A Phase 3, Multicenter, Randomized, Single-blind Clinical Trial (SUNSHINE). Clin Infect Dis. 2020; 71 (10): 2581–8	
112	Tillotts Pharma UK Ltd	Evidence review	215	24	We recommend that the draft guideline contains at least some reference to the phenomenon of vancomycin resistant enterococci (VRE). According to the ESCMID guidelines, although vancomycin is effective in the treatment of CDI, it is a broader-spectrum agent that causes significant disruption of the commensal colonic microbiota. A disruption in the commensal microbiota may predispose to recurrent CDI and intestinal colonisation by	Thank you for your comment. Following stakeholder consultation, the committee discussed the development of drug-resistant bacteria, in particular vancomycin resistant enterococci, but heard expert testimony and agreed that this is not a major concern in clinical practice when vancomycin is used orally for treating *C. difficile* infection. The committee remained of the opinion that the evidence supported vancomycin as the most cost-effective first-

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					healthcare-associated pathogens such as VRE and *Candida* species. Fidaxomicin appears to cause less disruption of the anaerobic colonisation microbiota and has activity against many VRE strains so it is suggested that the risk of colonization with and transmission of VRE associated with fidaxomicin treatment may be lower compared with vancomycin therapy. In a report by Gidengil et al 2014, the authors note that vancomycin is not recommended as a first line treatment for CDI by the US Centre for Disease Control due to 'selection' for strains of vancomycin-resistant enterococci, which can lead to invasive infections with substantial risk to patients and additional cost to the NHS. **References** DeBast SB et al. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection. Clin Microbiol Infect 2014; 20 (Suppl. 2): 1–26 Gidengil CA et al. Comparative Effectiveness of Fidaxomicin for Treatment of Clostridium Difficile Infection. Am J Pharm Benefits. 2014; 6 (4): 161-170	line option, and therefore this has been retained in the final recommendations. De Bast et al. 2014 is a European guideline and not an eligible study type (not a randomised controlled trial or systematic review). The study by Gidengil et al. 2014 is not an eligible study type (not a randomised controlled trial or systematic review).
113	Tillotts Pharma UK Ltd	Evidence review	247	13	We are concerned that the estimated cost of hospitalisation per CDI patient of £7,713 may significantly underestimate the actual figure. The economic model uses cost data from a study published in 2017 (Wilcox et al) but that study uses costing data from 2013/2014. The adjustment for inflation applied to the Wilcox	Thank you for your comment. We agree with your point that the data from the Wilcox et al. 2017 study were not inflated correctly. This has been corrected, and a new version of the analyses run using the corrected value of £8,173, rather than the initial one of £7,713. There were no

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					data appears to have been done from 2017/18 rather than 2013/14, meaning this figure is too low. In an analysis by Tresman and Goldenberg in 2018, length of hospital stay and costs were assessed for both first and recurrent episodes of C diff infection. This study does not appear to have been included in the committee's analysis despite being conducted in an NHS establishment. The key findings were that mean hospital stay for first infection was 17 days and for recurrent episodes was 33 days. Furthermore, they reported that mean total costs of hospitalisation for a first infection were £12,710 and for a recurrent infection £31,121. This micro-costing study utilises patient-level data for all direct and indirect costs, obtained from the hospital Patient, Education and Research Costing System (PERCS) and, unlike other studies that used accounting costs based on average tariffs, provides an accurate measure of the true burden of disease. There is a substantial difference in these figures to those used by the reviewing committee and it is likely that the recommendations in this draft guideline would change based upon these cost analyses. We therefore urge the committee to consider these more recent and detailed data, revise the economic model accordingly and recalculate the relative costs of the treatment	qualitative differences to the conclusions as a result of this correction with, as an example, the ICER for first-line fidaxomicin versus first-line vancomycin reducing from approximately £155,000 to £151,000, still well above NICE's cost-effectiveness threshold. These new results are now reported in appendix N of the evidence review. The committee considered the Tresman study (2018) as a possible alternative source of cost data for hospitalisation associated with recurrence. They agreed it was a less appropriate source than the Wilcox study for 3 key reasons: • Tresman and Goldenburg et al. studies were from a single centre and contained 45 people. Wilcox et al. was a multi-centre study and contained 64 people. • Tresman and Goldenburg et al. included children (it is unclear how many, but they were within the inclusion criteria), which is out of scope for the model and would increase the average cost (paediatric care costs are generally higher than adult inpatient costs). • Tresman and Goldenburg et al. included costs for the depreciation of buildings and other overheads which contribute to the higher values, and would not be expected to meaningfully

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					options, as failure to include these more detailed and recent costs risks invalidating the guidance. **References** Tresman R and Goldenberg SD. Healthcare resource use and attributable cost of Clostridium difficile infection: a micro-costing analysis comparing first and recurrent episodes. J Antimicrob Chemother 2018; 73: 2851–2855 Wilcox MH et al. Impact of recurrent Clostridium difficile infection: hospitalization and patient quality of life. The Journal of antimicrobial chemotherapy. 2017; 72 (9): 2647-56.	change based on the clinical differences being modelled. The cost-effectiveness analysis has therefore continued to use the study by Wilcox et al. to inform the costs of hospitalisation associated with recurrence.
114	Tillotts Pharma UK Ltd	Evidence review	254	6	We are concerned that the price of vancomycin is not accurately reflected in the evidence review and hence, the economic model needs to be updated to include the accurate Drug Tariff price for vancomycin. The price cited for vancomycin 125mg capsules were derived from the NHS eMIT database. This database provides weighted average prices and the database is based on data for 12 months up to the end of 2019. In comparison, fidaxomicin price information was obtained from the Drug Tariff. This is therefore an unbalanced comparison using out of date data. In Table 60 (page 254), the price for a pack of 28 vancomycin 125mg capsules is £51.69. The price of vancomycin 125mg capsules (28 pack) in the Drug Tariff is £132.47 at the time of writing (February 2021). This is	Thank you for your comment. The prices used have followed the approach specified in the Developing NICE guidelines: the manual. Specifically, for medicines primarily prescribed in secondary care (as the committee agreed was relevant here): "Analyses based on price reductions for the NHS will be considered only when the reduced prices are transparent and can be consistently available across the NHS, and when the period for which the specified price is available is guaranteed. When a reduced price is available through a patient access scheme that has been agreed with the Department of Health and Social Care, the analyses should include the costs associated with the scheme. If the price is not listed on eMIT, then the current price listed on the British National Formulary

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					substantially higher than the price cited in the evidence review. This must be corrected and the economic model recalculated to inform the recommendations in the guideline. In the period between the beginning of this review and now, the ownership of the marketing authorisation for fidaxomicin has changed. The new owner of the MA is Tillotts Pharma UK Ltd, and Tillotts are willing to enter into patient access agreements with organisations of the NHS to further improve the cost effectiveness of fidaxomicin. **References** NHS Electronic Drug Tariff. February 2021 edition. Accessed online February 2021	(BNF) should be used." Therefore, with a price for vancomycin available on eMIT but not a price for fidaxomicin, the correct sources of data on price have been used. For completeness, an additional sensitivity analysis was conducted using the BNF price for vancomycin (£132.47 vs. £51.69). This resulted in an ICER for FID-VAN versus VAN-FID of £117,000 (original ICER £151,000 [including the correction to inflation of hospitalisation costs]), and therefore vancomycin would remain the most cost-effective treatment option. The results of these additional analyses are provided in appendix N of the evidence review. NICE guidelines, unlike technology appraisals, do not include negotiations on price or patient access schemes as part of their process. However, should the published list price for fidaxomicin change in the future, this would of course need to be reflected in any future updates of the guideline.
115	Tillotts Pharma UK Ltd	Evidence review	254	7	As noted in the point above (Comment 11), we are extremely concerned that the price data for vancomycin capsules is inaccurate. We agree with the conclusion that two packs of vancomycin are required for a course of treatment of CDI. Therefore, the total cost for a treatment course using vancomycin should be £264.94,	Thank you for your comment. The prices used have followed the approach specified in Developing NICE guidelines: the manual. Specifically, for medicines primarily prescribed in secondary care (as the committee agreed was relevant here): "Analyses based on price reductions for the NHS will be considered only when the

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					based on the corrected Tariff price of £132.47 per pack. This is substantially higher than the figure of £103.38 as stated in Table 61 (page 254) of the evidence review.	reduced prices are transparent and can be consistently available across the NHS, and when the period for which the specified price is available is guaranteed. When a reduced price is available through a patient access scheme that has been agreed with the Department of Health and Social Care, the analyses should include the costs associated with the scheme. If the price is not listed on eMIT, then the current price listed on the British National Formulary (BNF) should be used." Therefore, with a price for vancomycin available on eMIT but not a price for fidaxomicin, the correct sources of data on price have been used. For completeness, an additional sensitivity analysis was conducted using the BNF price for vancomycin (£132.47 per pack versus £51.69 per pack). This resulted in an ICER for FID-VAN versus VAN-FID of £117,000 (original ICER £151,000 [including the correction to inflation of hospitalisation costs]), and therefore vancomycin would remain the most cost-effective treatment option.
116	Tillotts Pharma UK Ltd	Economic model	NA	NA	We are very concerned that mortality as a consequence of recurrence of infection is not included in the economic model, especially as higher mortality rates are associated with recurrence of CDI. On review of the model we feel there is a significant omission in the decision tree element of the model.	Thank you for your comment. The committee agreed that issues around mortality were important, and therefore discussed these matters in some depth. First, they noted that there was no evidence of mortality differences from the randomised controlled trials, and that most models of *C. difficile* therefore did not

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					Acute mortality is limited to the first decision tree only (initial CDI) but there is no consideration of mortality for recurrent CDI (*S*ee Evidence Review page 249, lines 2-8). The mortality rates used in the model are based on 30 day all-cause fatality rates, reported by Public Health England. Although not explicit within the text, the model looks up an age-associated 30 day all-cause fatality rate. In the base case this is for a 63 year old returning a rate of 7.75%. We believe this application of the PHE data is inappropriate as there is no consideration on the distribution of the age in the current approach. It is therefore highly likely that the model underestimates the true mortality of CDI infections. In the same PHE data source, detailed in the report/model, a mean case fatality rate following CDI of 13.5 is reported (Table S21 – 30 day all cause mortality). This is much higher than the current figure used and is likely to better reflect the true mortality of CDI in the NHS. According to the draft guideline, the definition of recurrence is CDI occurring more than 12 weeks after symptom resolution. Therefore, we feel that the current approach, using 30 day mortality rates in the initial CDI, does not appropriately capture mortality associated with recurrent CDI and as such significantly underestimates the clinical benefit of fidaxomicin which reduces the likelihood of recurrence.	assume any mortality differences between different antibiotics. They also noted the model does already include some post-recurrence mortality, in the form of people who die as a result of fulminant colitis. Nonetheless, they agreed some additional analyses exploring various assumptions around mortality would be useful. First, consideration was given to the baseline mortality used for the initial *C. difficile* infection. To address concerns that the value of 7.7% may have been an underestimate, an additional analysis was conducted using a mortality of 11.8% (the value for the 65-74 age range). This change resulted in no meaningful differences in the ICER for first-line fidaxomicin versus first-line vancomycin. Second, the issue of potentially reduced recurrence mortality with fidaxomicin was discussed. The committee agreed it was inappropriate to simply apply the baseline mortality rates at each recurrence, as this risked double counting some deaths (if recurrence occurs within 30 days), and that the limited evidence available did not suggest mortality risks were equivalent at each recurrence. They agreed that given the large differences to cost-effectiveness that result from changes in the assumptions around mortality, it was important that any results generated be

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					We have attempted to modify the model to incorporate mortality associated with recurrent CDI, utilising the same 30 day mortality rates as the initial CDI, and the impact on the ICER results are substantial. In our exploratory analysis when comparing vancomycin 1st line then fidaxomicin 2nd line to fidaxomicin 1st line then vancomycin 2nd line (and keeping all other assumptions at the default settings) the ICER reduced from £155,527 per QALY to £11,501 per QALY, demonstrating that inclusion of mortality in recurrent events could be a significant driver of cost-effectiveness. This revised QALY calculation includes the currently assumed (default) costs of hospitalisation (see Comment 10). In addition to the likely underestimation of CDI mortality rates, as detailed above, the use of the same 30 day mortality rates, currently reported in the model, for recurrent CDI could be considered conservative. Patients who experience a recurrent event are likely to be in poor health, following the initial infection, and as such the risk of mortality may be increased. Data from Olsen et al 2015 confirms that mortality is associated with recurrence of infection (36% at 180 days) and is greater than that associated with first infection (26% at 180 days). Other authors report similar findings, confirming that recurrent disease is associated with higher mortality than the initial CDI episode. This further highlights the	based on published quantitative data on the impacts of recurrence on mortality. They therefore focused their exploratory analyses around the Olsen et al. 2015 paper you cite. The hazard ratio reported in that paper was used to estimate excess mortality associated with recurrence, and then this was applied in the model in two different ways, one splitting that mortality across multiple potential rounds of recurrence, and one assuming it is all associated with the first recurrence. As would be expected, this analysis makes fidaxomicin considerably more cost-effective (although remaining above the standard thresholds), with the ICER reducing to around £49,000/QALY if deaths are spread across recurrences, and £32,000/QALY if all applied to the first recurrence (full details of all these analyses are available in the evidence review). The committee noted, however, that these analyses were likely to be extremely favourable to fidaxomicin (or at least not possible to validate as being appropriate to this specific decision problem). First, the Olsen et al. study was based on data from 2003-2009 in the USA, and it is not clear they can be appropriately extrapolated to the current UK population. Second, this approach relies on the assumption that the direction of causation is entirely from more

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					significance of not considering mortality in recurrent CDI events. Since the model fails to capture all direct health effects, we feel that it does not meet the NICE Reference Case and would request that the model be reviewed and the mortality for recurrent CDI be included as a matter of urgency. We have included our modified version of the model with our submission for your reference. **References** Olsen MA et al. Recurrent Clostridium difficile infection is associated with increased mortality. Clin Microbiol Infect. 2015; 21: 164–170 Public Health England. Thirty-day all-cause mortality following MRSA, MSSA and Gram-negative bacteraemia and C. difficile infections. April 2019 to March 2020	recurrences causing more deaths. An alternative hypothesis is that there are underlying factors (for example frailty or comorbidities) that make a person more likely both to die and relapse, and that cannot be entirely adjusted for in the Olsen et al. study. If this is the case, then this analysis will be overestimating the mortality benefits from fidaxomicin. Additionally, since deaths from fulminant colitis are still included in the model, there will be some double counting of deaths, which again will favour fidaxomicin. Taking all these limitations into account, and considering the fact the ICER still remained above £30,000/QALY even with these assumptions, the committee agreed none of these new analyses provided convincing evidence that fidaxomicin could be more cost-effective than vancomycin as a first-line treatment option, and therefore no changes were made to that recommendation.
117	Betsi Cadwaladr University Healthboard	Guideline	2	15 & 16	We would consider that other medications such as laxatives & anti-motility agents should also be reviewed with suspected or confirmed *C.difficile* infection and included within the list.	Thank you for your comment. The recommendation has been amended to include reviewing the need to continue treatment with other medicines with gastrointestinal activity or adverse effects, such as laxatives. This includes antimotility medicines.

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118	Betsi Cadwaladr University Healthboard	Guideline	2	11	Would it be possible to define the specific co-morbidities that may affect risk of complications?	Thank you for your comment. The committee recognised the importance of assessing individual patient factors, such as any comorbidities. However, they did not want to give more specific details, as this may be interpreted as an exhaustive list of comorbidities which may affect the risk of complications or recurrence. This would need to be based on clinical judgment.
119	Betsi Cadwaladr University Healthboard	Guideline	5	19	We would consider a total of 14 days of Vancomycin 125mg QDS more of an acceptable duration given that pack sizes are available as 28 capsules – this would prevent the need for having to pack down supply and may prevent any challenges within primary care.	Thank you for your comment. The committee recognised the issue with pack sizes, however they agreed that the shortest course that is likely to be effective should be prescribed to minimise the risk of antimicrobial resistance. The randomised trials included in the clinical evidence based for this guideline all used a 10 day rather than 14 day dosing schedule, and therefore the committee agreed this was the one it would be appropriate to recommend. This is also the standard licensed dose (see the vancomycin summary of product characteristics).
120	Betsi Cadwaladr University Healthboard	Guideline	5	19	Should the treatment recommendation table also specify an option for patients who also require concomitant antibiotics? – Fidaxomicin is typical standard practice in these situations.	Thank you for your comment. The committee discussed this and amended the recommendations to clarify that any existing antibiotic being taken should be stopped unless it is essential. If an antibiotic is still essential, health professionals should consider changing to one with a lower risk of causing *C. difficile* infection. They also agreed that for people

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						in the community, prescribers should consider seeking prompt specialist advice from a microbiologist or infectious diseases specialist before starting treatment, and this has been added to the recommendation. Specialists would be able to advise on this situation, if continuing existing antibiotic treatment was essential.
121	Betsi Cadwaladr University Healthboard	Guideline	General	General	Does the group have any guidance around how soon / urgently it's advised to start *C.difficile* treatment following positive diagnosis? – Concerned that PO Vancomycin might not be readily available immediately within community pharmacies as not typically stocked. Would starting treatment within 24 hours of diagnosis be acceptable?	Thank you for your comment. The committee discussed whether they could give further information about when treatment should be started. As with all infections that require antibiotics, treatment should be started as soon as possible. Following discussion, they agreed that for people in the community, prescribers should consider seeking prompt specialist advice from a microbiologist or infectious diseases specialist before starting treatment, and this has been added to the recommendation. From their experience, the committee agreed that it was uncommon for people to present in the community with *C. difficile* infection, with GP committee members seeing very few cases. The committee recognised that there are some implementation challenges for this guideline. Local health organisations, health and social care practitioners and other stakeholders will need to work

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						collaboratively to ensure that appropriate treatment is available in primary care for people with suspected or confirmed *C. difficile* infection. NICE are working with other national stakeholders such as NHS England and Improvement (including procurement teams) to support implementation of the guideline.
122	Royal Pharmaceutical Society	Evidence review	General	General	The use of oral vancomycin as first line treatment will be a change for many, both in hospital and community settings, with cost implications if replacing metronidazole. A clear comparison between metronidazole and vancomycin for first line treatment and the reasons to switch from metronidazole to vancomycin would be helpful as this is the key recommendation that clinicians will note within the guideline. A licensed oral solution of vancomycin is not currently available and while the vials for reconstitution can be used this is not a good practical option for community settings.	Thank you for your comment. The use of metronidazole was one of the options tested in the cost-effectiveness modelling used to underpin this guideline. When the costs of rehospitalisation were included in the analysis, the committee agreed the results were clear that vancomycin was a more cost-effective first-line treatment than metronidazole, and that it was dominant in most scenarios (meaning the use of vancomycin is both less costly and more effective than the use of metronidazole). These results are based on the clinical evidence review, which showed that metronidazole has both lower initial cure rates and higher recurrence rates than vancomycin. Following stakeholder consultation, they agreed that for people who cannot take oral medicines, specialist advice should be sought from a gastroenterologist or pharmacist about alternative enteral routes for antibiotics. This has been added to the recommendation. NICE are working with other national stakeholders such as NHS

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						England and Improvement (including procurement teams) to support implementation of the guideline.
123	Royal Pharmaceutical Society	Evidence review	General	General	Ensuring timely access to both vancomycin and fidaxomicin in out-of-hospital care settings is a concern and will need consideration when implementing the final guidance.	Thank you for your comment. From their experience, the committee agreed that it was uncommon for people to present in the community with *C. difficile* infection, with GP committee members seeing very few cases. The committee recognised that there are some implementation challenges for this guideline. Local health organisations, health and social care practitioners and other stakeholders will need to work collaboratively to ensure that appropriate treatment is available in primary care for people with suspected or confirmed *C. difficile* infection. NICE are working with other national stakeholders such as NHS England and Improvement (including procurement teams) to support implementation of the guideline.
124	Royal Pharmaceutical Society	Visual summary	1	-	In the *Assessment* section, severity assessment is recommended but it does not then link to different treatment depending on severity. Some more detail on actions required based on severity assessment would be helpful.	Thank you for your comment. The committee agreed that the main reason to assess severity was to identify the appropriate place of care and overall management. The committee agreed that the recommendation should include an assessment of whether the current infection was a first or subsequent (recurrent) episode. This was because it was a driver in the economic model and determines the antibiotic choice.

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						Following stakeholder consultation, in addition to seeking specialist advice, high-dose oral vancomycin plus intravenous metronidazole has been added to the prescribing table (agreed by committee consensus) as a specialist option for treating a life-threatening infection. This also supports the need to assess the severity of infection.
125	Royal Pharmaceutical Society	Visual summary	1	-	In the *Prescribing considerations* section, should concurrent prescriptions for prokinetics, laxatives and opiates also be mentioned? We suggest changing 'proton pump inhibitors' to 'gastric acid suppressing agents' or adding 'H2-antagonists'.	Thank you for your comment. The recommendation has been amended to include reviewing the need to continue treatment with other medicines with gastrointestinal activity or adverse effects, such as laxatives. This includes prokinetic, opiate and histamine antagonist medicines. The committee preferred to retain proton pump inhibitors as a separate bullet point in the recommendation. This is because the literature search included proton pump inhibitors and some associations have been made between their use and the risk of *C. difficile* infection or recurrence.
126	Royal Pharmaceutical Society	Visual summary	1	-	*Treating CDI* section – it seems strange to mention bezlotoxumab and FMT but not mention antibiotics that should be used for initial treatment and recurrence.	Thank you for your comment. The visual summary is published in a consistent format for all NICE antimicrobial prescribing guidelines and includes a summary of all recommendations. This format has been very well received by users. The antibiotic prescribing table is presented on 1 side (page 2), with the remaining guideline content summarised on the other side (page 1).

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127	Royal Pharmaceutical Society	Visual summary	1	-	*Preventing CDI* section – We think it is unlikely that clinicians would consider offering prebiotics or probiotics as they are not medicines. Consider writing instead 'Advise patient not to use prebiotics or probiotics as they are not effective'.	The committee agreed that there is some evidence (with many limitations) of a small effect with probiotics in preventing *C. difficile* infection. However, because of concerns about the evidence base they could not identify any scenario when the use of probiotics could be recommended in people taking antibiotics. Following stakeholder consultation, the recommendation has been amended so that it focuses on the advice given to people and states 'Do not advise people taking antibiotics to take prebiotics or probiotics to prevent *C. difficile* infection'.
128	British Society for Antimicrobial Chemotherapy				No comments	Thank you.
129	Public Health Wales	Guideline	1	Line 4 in the box	Remove 'aged 72 hours or over' as nonsensical	Thank you for your comment. This is standard for all antimicrobial prescribing guidelines which apply only for people aged 72 hours or over
130	Public Health Wales	Guideline	2	13	Review with consideration of de-escalating or stopping treatment. Examples of de-escalation include reducing dose, or reducing pharmacological response (such as switching from proton pump inhibitors to histamine antagonists)	Thank you for your comment. No evidence was identified from the literature search on the effect of stopping or de-escalating proton pump inhibitors. However, the committee recognised the importance of reviewing the need to continue any treatment with proton pump inhibitors, and this is included in the recommendations.
131	Public Health Wales	Guideline	2	16	Add 'opiates', 'prokinetics', 'laxatives', and change 'proton pump inhibitors' to 'gastric acid suppressing agents'	Thank you for your comment. The recommendation has been amended to include reviewing the need to continue treatment with other medicines with gastrointestinal activity or adverse effects,

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						such as laxatives. This includes prokinetic, opiate and histamine antagonist medicines. The committee preferred to retain proton pump inhibitors as a separate bullet point in the recommendation. This is because the literature search included proton pump inhibitors and some associations have been made between their use and the risk of *C. difficile* infection or recurrence.
132	Public Health Wales	Guideline	6	Table, top line	Define 'ineffective'. Along with 'treatment failure', this could be interpreted as not responding to treatment within a specific time period, therefore to avoid overuse of this drug, both these statements need to be defined in terms of what is considered to be a reasonable time period	Thank you for your comment. This has been clarified in the prescribing table (table 1) which states 'Use clinical judgement to determine whether antibiotic treatment for C. difficile infection is ineffective. It is not usually possible to determine this until day 7 because diarrhoea may take 1 to 2 weeks to resolve'.
133	Public Health Wales	Guideline	9	16-27	Consideration needs to be made when switching from a more effective agent to a less effective agent, such as switching from a proton pump inhibitor to a histamine antagonist, as a means of de-escalating treatment. Consideration should be made to refer to a gastroenterologist for this decision.	Thank you for your comment. No evidence was identified from the literature search on the effect of stopping or de-escalating proton pump inhibitors. However, the committee recognised the importance of reviewing the need to continue any treatment with proton pump inhibitors, and this is included in the recommendations. Following discussion, the committee agreed that for people in the community, prescribers should consider seeking prompt specialist advice from a microbiologist or infectious diseases specialist before starting treatment, and

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						this has been added to the recommendation.
134	Public Health Wales	Guideline	16-17		Metronidazole. Much of the evidence submitted here is based on expert opinion from committee members, and given the increased cost of vancomycin and especially fidaxomicin, it is expected that there will be significant resistance to change in primary care. A clearer comparison between metronidazole and vancomycin for first line treatment and the reasons to switch from met to vanc would therefore be very helpful	Thank you for your comment. The use of metronidazole was one of the options tested in the cost-effectiveness modelling used to underpin this guideline. When the costs of rehospitalisation were included in the analysis, the committee agreed the results were clear that vancomycin was a more cost-effective first-line treatment than metronidazole, and that it was dominant in most scenarios (meaning the use of vancomycin is both less costly and more effective than the use of metronidazole). These results are based on the clinical evidence review (including a number of randomised controlled trials on these options), which showed that metronidazole has both lower initial cure rates and higher recurrence rates than vancomycin.
135	Public Health Wales	Visual summary	1	First column	In Prescribing considerations, please consider adding 'prokinetics', 'laxatives', 'opiates', and changing 'proton pump inhibitors' to 'gastric acid suppressing agents'. Instead of reviewing the need to continue, please consider reviewing with consideration of de-escalating or stopping treatment, with suitable referral to specialists such as microbiology, infectious diseases, gastroenterology, acute pain team or others as necessary.	Thank you for your comment. The recommendation has been amended to include reviewing the need to continue treatment with other medicines with gastrointestinal activity or adverse effects, such as laxatives. This includes prokinetic, opiate and histamine antagonist medicines. The committee preferred to retain proton pump inhibitors as a separate bullet point in the recommendation. This is because the literature search included proton pump inhibitors and some associations have

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						been made between their use and the risk of *C. difficile* infection or recurrence. There was no evidence to suggest a preferred way to stop or reduce the dose of proton pump inhibitors, or on the effect of changing to a histamine antagonist. However, the committee recognised the importance of reviewing the need to continue any treatment with proton pump inhibitors, and this is included in the recommendations. Following discussion, the committee agreed that for people in the community, prescribers should consider seeking prompt specialist advice from a microbiologist or infectious diseases specialist before starting treatment, and this has been added to the recommendation.
136	Public Health Wales	Visual summary	1	Middle column bottom box	Preventing CDI. Not helpful as no positive interventions listed. Can this box be used to emphasise the need to review the need for any antimicrobials prescribed and to choose a narrow agent where possible to minimise the risk of acquiring CDI?	Thank you for your comment. Infection control procedures and antimicrobial stewardship is outside the scope of this guideline. The guideline now signposts to other relevant national guidance in the 'Preventing *C. difficile* infection' section, which cover these aspects – Public Health England's guidance on *C. difficile* infection: how to deal with the problem, NICE's guidance on healthcare-associated infections and NICE's guidance on antimicrobial stewardship.

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137	Public Health Wales	Visual summary	2	First row: life threatening	Seek specialist advice. Can this be expanded to include advice from gastroenterology or colorectal surgeons where ileus or toxic megacolon is suspected? Also, need for further investigation such as CT of abdomen?	Thank you for your comment. Surgical interventions are outside the scope of this guideline. However, a recommendation has been added to ensure people in hospital with suspected or confirmed *C. difficile* infection have care from a multidisciplinary team that includes a microbiologist or infectious diseases specialist, gastroenterologist, surgeon, pharmacist and dietitian, as needed.
138	Public Health Wales	Visual summary	2	Third row: if vanc is ineffective	Define 'ineffective', in terms of clinical markers of deterioration, or how long current treatment should progress without clinical improvement, before the treatment is reviewed or escalated.	Thank you for your comment. This has been clarified in the prescribing table (table 1) which states 'Use clinical judgement to determine whether antibiotic treatment for C. difficile infection is ineffective. It is not usually possible to determine this until day 7 because diarrhoea may take 1 to 2 weeks to resolve'.
139	Public Health Wales	Guideline and visual summary	General	General	In assessing the severity of infection and when to refer to secondary care, it would be helpful for primary care prescribers if there was more clarity on how to clinically assess severity, especially given some GPs may only see one or two cases a year. Is there a list of red flags that can be incorporated, both for prescribers and patients?	Thank you for your comment. Diagnosis of *C. difficile* infection is outside the scope of this guideline. Users are signposted to Public Health England's guidance on diagnosis and reporting. The severity of infection definitions (mild, moderate, severe and life-threatening) are included the 'Terms used in the guideline' section, and are also from Public Health England's guidance.
140	Public Health Wales	Guideline and visual summary	General	General	This guideline represents a major shift away from metronidazole, which has been traditionally recommended for mild CDI, to vancomycin and fidaxomicin. Both drugs are	Thank you for your comment. The use of metronidazole was one of the options tested in the cost-effectiveness modelling used to underpin this guideline. When the

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					significantly more expensive and GPs may lack experience and confidence in prescribing these drugs. The case for moving away from metronidazole therefore needs to be stronger / clearer, as there will be significant resistance to change.	costs of rehospitalisation were included in the analysis, the committee agreed the results were clear that vancomycin was a more cost-effective first-line treatment than metronidazole, and that it was dominant in most scenarios (meaning the use of vancomycin is both less costly and more effective than the use of metronidazole). These results are based on the clinical evidence review (including a number of randomised controlled trials on these options), which showed that metronidazole has both lower initial cure rates and higher recurrence rates than vancomycin.
141	Public Health Wales	Guideline and visual summary	General	General	As mentioned above, cost is also an issue and many GPs will be reluctant to prescribe vancomycin or fidaxomicin. Consideration has to be given to how prescribing and dispensing of these drugs is going to work in practice. Given how rarely these drugs are likely to be used, it is unlikely that an individual community pharmacy will be prepared to stock these drugs, which could lead to a delay in treatment. Examples of primary care implementation should be provided, such as an enhanced payment to selected community pharmacies to keep as stock, as in palliative care, or a service level agreement between primary and secondary care such that fidaxomicin could be provided from the local hospital.	Thank you for your comment. From their experience, the committee agreed that it was uncommon for people to present in the community with *C. difficile* infection, with GP committee members seeing very few cases. They recognised the importance of additional support for primary care prescribers who may be unfamiliar with the recommended antibiotics. Following discussion, they agreed that for people in the community, prescribers should consider seeking prompt specialist advice from a microbiologist or infectious diseases specialist before starting treatment, and this has been added to the recommendation. The committee recognised that there are some implementation challenges for this

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						guideline. Local health organisations, health and social care practitioners and other stakeholders will need to work collaboratively to ensure that appropriate treatment is available in primary care for people with suspected or confirmed *C. difficile* infection. NICE are working with other national stakeholders such as NHS England and Improvement (including procurement teams) to support implementation of the guideline.
142	Public Health Wales	Guideline and visual summary	General	General	Finally, regarding the wholesale switch from metronidazole to vancomycin as first line treatment, there is local concern that this will drive the development and acquisition of vancomycin resistant *Enterococci* (VRE).	The use of metronidazole was one of the options tested in the cost-effectiveness modelling used to underpin this guideline. When the costs of rehospitalisation were included in the analysis, the committee agreed the results were clear that vancomycin was a more cost-effective first-line treatment than metronidazole, and that it was dominant in most scenarios (meaning the use of vancomycin is both less costly and more effective than the use of metronidazole). These results are based on the clinical evidence review, which showed that metronidazole has both lower initial cure rates and higher recurrence rates than vancomycin. Following stakeholder consultation, the committee discussed the development of drug-resistant bacteria, in particular vancomycin resistant enterococci. They heard expert testimony and discussed further, and agreed that this is not a major

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						concern in clinical practice when vancomycin is used orally for treating *C. difficile* infection. The committee remained of the opinion that the evidence supported vancomycin as the most cost-effective first-line option, and therefore this has been retained in the final recommendations.
143	Public Health Wales	Guideline	General	General	Faecal transplant is mentioned as an option in difficult to treat cases but all the clinical comparisons are with vancomycin. In reality, this treatment option is likely to compete with fidaxomicin in secondary care. Is there any direct clinical evidence comparing these two regimes and how does the prescriber choose on the basis of clinical efficacy?	Thank you for your comment. No study included in the evidence review compared fidaxomicin with faecal microbiota transplant (FMT). The included trial comparators were placebo in 1 study and vancomycin in the remaining studies. When assessing the evidence, the committee noted that most studies comparing different antibiotics were in initial infections or first recurrences, whilst most studies on FMT were in people with 3-4 or more recurrences, with a gap between those 2 sets of evidence. The committee therefore agreed it was not possible currently to provide guidance on at what exact stage in the pathway FMT becomes superior to antibiotics (and in particular fidaxomicin), and this would have to be left to individual clinician judgement.
144	Public Health Wales	Guideline and visual summary	General	General	This guideline is designed for secondary as well as primary care use yet the only option offered for fulminant / life threatening CDI is oral. This is a major gap.	Thank you for your comment. In the draft guideline for consultation, no antibiotic options were given for treating life-threatening C. difficile infection. Following stakeholder consultation, in

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						addition to seeking specialist advice, high-dose (500 mg) oral vancomycin with intravenous metronidazole has been added to the prescribing table (agreed by committee consensus) as a specialist option for treating life-threatening *C. difficile* infection. The committee discussed the most appropriate route of administration of antibiotics for *C. difficile* infection. They agreed that the enteral route is best because sufficient concentrations within the intestinal lumen need to be reached. The committee concluded that it is preferable to give antibiotics via the oral route or, if this is not possible, enterally in some other way (such as a nasogastric or enteral feeding tube, or rectally). Following stakeholder consultation, they advised seeking specialist advice on administration from a gastroenterologist or pharmacist if the oral or another enteral route is not available.
145	Public Health Wales	Guideline	General	General	Where the patient has severe disease with possible ileus or toxic megacolon, there should be greater emphasis on the need to refer to other procedures, such as a gastro or surgical consult. With the lack of surgical intervention in this document, the risk is that prescribers could attempt to treat a patient with an antimicrobial where surgical intervention such as colectomy would be more appropriate. Is the panel / committee	Thank you for your comment. A direct comparison between faecal microbiota transplant (FMT) and fidaxomicin is not possible as there were no studies in which they were compared. Surgical interventions such as colectomy are outside the scope of this guideline. However, a recommendation has been added to ensure people in hospital with

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					able to compare directly between fidaxomicin, faecal transplant and colectomy in severe disease?	suspected or confirmed *C. difficile* infection have care from a multidisciplinary team that includes a surgeon, as needed.
146	Public Health Wales	Guideline and visual summary	General	General	Terms such as 'ineffective' are used throughout both documents but is it possible to better define treatment failure or deterioration in terms of clinical outcomes / markers and with timelines? This would better help prescribers determine when it is appropriate to escalate treatment or seek specialist referral.	Thank you for your comment. This has been clarified in the prescribing table (table 1) which states 'Use clinical judgement to determine whether antibiotic treatment for C. difficile infection is ineffective. It is not usually possible to determine this until day 7 because diarrhoea may take 1 to 2 weeks to resolve'.
147	Public Health Wales	Guideline and visual summary	General	General	Patients in primary care who are nil by mouth, with or without a nasogastric or percutaneous gastric tube are of particular concern, as there is currently no option to treat other than admitting to secondary care. Most patients and carers will be unable to manipulate a vancomycin vial. Is there any other oral option or should this cohort of patients explicitly be referred to secondary care?	Thank you for your comment. The committee discussed the most appropriate route of administration of antibiotics for *C. difficile* infection. They agreed that the enteral route is best because sufficient concentrations within the intestinal lumen need to be reached. The committee concluded that it is preferable to give antibiotics via the oral route or, if this is not possible, enterally in some other way (such as a nasogastric or enteral feeding tube, or rectally). Following stakeholder consultation, they advised seeking specialist advice on administration from a gastroenterologist or pharmacist if the oral or another enteral route is not available.
148	Public Health Wales	Guideline and visual summary	General	General	Patients are advised to drink enough to avoid dehydration in active CDI. Is there evidence to suggest advising patients to use oral electrolyte solutions? Should this be a best practice point?	Thank you for your comment. Use of oral electrolyte solutions was outside the scope of this guideline.

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149	Public Health Wales	Guideline and visual summary	General	General	Given the costs associated with implementing this guideline, is it possible to negotiate at a UK level to provide additional funding to local health boards and NHS trusts to allow / support this guidance to be adopted? Without additional funding, the uptake of this guidance is likely to be poor.	Thank you for your comment. Unfortunately, these sorts of negotiations are not something that are within the remit of NICE to comment on. However, as well as the cost-effectiveness work undertaken, NICE will also be producing a resource impact tool alongside the guideline, which will estimate the additional costs associated with using vancomycin and fidaxomicin for this indication. The committee recognised that there are some implementation challenges for this guideline. Local health organisations, health and social care practitioners and other stakeholders will need to work collaboratively to ensure that appropriate treatment is available for people with suspected or confirmed *C. difficile* infection. NICE are working with other national stakeholders such as NHS England and Improvement (including procurement teams) to support implementation of the guideline.
150	Public Health Wales	Guideline and visual summary	General	General	Has there been any discussion at a UK level with the manufacturers of vancomycin capsules and fidaxomicin, to ensure that if this guideline is widely adopted, sufficient stock will be available with supply chain?	Thank you for your comment. Based on stakeholder comments, there is no suggestion that implementation of the guideline would result in medicines shortages. In many areas, vancomycin and fidaxomicin are already used routinely in practice for treating *C. difficile* infection. The committee recognised that there are some implementation challenges for this

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						guideline. Local health organisations, health and social care practitioners and other stakeholders will need to work collaboratively to ensure that appropriate treatment is available for people with suspected or confirmed *C. difficile* infection. NICE are working with other national stakeholders such as NHS England and Improvement (including procurement teams) to support implementation of the guideline.
151	Public Health Wales	Guideline and visual summary	General	General	There is mention of reviewing at 3 – 5 days but no mention of when to stop treatment. Do we complete the course regardless of clinical response and if not, is there evidence of when to stop treatment based on clinical response? This would be more relevant in secondary care.	Thank you for your comment. The committee agreed that resolution of diarrhoea may not happen by day 3 to 5. This has been clarified in the prescribing table (table 1) which states 'Use clinical judgement to determine whether antibiotic treatment for C. difficile infection is ineffective. It is not usually possible to determine this until day 7 because diarrhoea may take 1 to 2 weeks to resolve'. The recommendation on reassessment has been amended to remove the 3 to 5 day time period. The standard licensed dose of oral vancomycin is recommended (125 mg four times a day for 10 days), in line with the vancomycin summary of product characteristics.
152	Public Health Wales	Guideline and visual summary	General	General	Finally, there is little usable information in terms of providing a quick, easy to use source of information to the prescriber on how to diagnose, treat and prevent CDI. The two	Thank you for your comment. The visual summary is published in a consistent format for all NICE antimicrobial prescribing guidelines and includes a

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					page visual summary provides a basic level of detail, and more is available in the guideline, consisting of 32 pages of linked statements, but this is not easy to use on the ward or in a busy surgery. It would be much more helpful if there were algorithms or tables summarising basic clinical diagnostics and definitions such as severity, when to escalate / de-escalate etc. as well as what to treat with and when. Could the two page visual summary be expanded to include these definitions and algorithms?	summary of all recommendations. This format has been very well received by users. The final guideline will also be published as a web-based document (rather than a flat text document), which will improve navigation for users. Diagnosis of *C. difficile* infection is outside the scope of this guideline. Users are signposted to Public Health England's guidance on diagnosis and reporting.
153	NHS England and NHS Improvement South West	General			This guidance is welcomed; the place of vancomycin first line with fidaxomicin second line will increase spend on antibiotics but should deliver reduced length of stay to offset that cost. Reduced number of relapse and recurrent cases will improve patient outcomes and quality of life, however routine case data capture for relapse/recurrent events is not robustly captured and not reported so impact of these changes to treatment will be hard to identify and evidence. Timely access to oral vancomycin and fidaxomicin in out of acute hospital care is a concern, especially in primary care settings.	Thank you for your comment in support of the recommended choices of antibiotics. From their experience, the committee agreed that it was uncommon for people to present in the community with *C. difficile* infection, with GP committee members seeing very few cases. The committee recognised that there are some implementation challenges for this guideline. Local health organisations, health and social care practitioners and other stakeholders will need to work collaboratively to ensure that appropriate treatment is available in primary care for people with suspected or confirmed *C. difficile* infection. NICE are working with other national stakeholders such as NHS England and Improvement (including

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						procurement teams) to support implementation of the guideline.
154	NHS England and NHS Improvement South West	Guideline	2	6-7	How to deal with the problem document refers to antibiotic treatment that does not align with this draft guidance. Will this old DH / HPA document be updated?	Thank you for your comment. This guideline on *C. difficile* infection: antimicrobial prescribing is published jointly by NICE and Public Health England. It will update any Public Health England guidance recommendations on treating *C. difficile* infection. Other aspects of these guidelines will be retained, for example recommendations on diagnosis and reporting. NICE will work closely with Public Health England to make sure this is clear for users.
155	NHS England and NHS Improvement South West	Guideline	2	10	Can the severity of infection be hyperlinked each time it is used in the guidance?	Thank you for your comment. A link has been added at each use.
156	NHS England and NHS Improvement South West	Guideline	2	9	Define recurrent in this place in guidance would be helpful	Thank you for your comment. This has been added to the 'Terms used in the guideline' section, and included below the prescribing table (table 1).
157	NHS England and NHS Improvement South West	Guideline	2	12	Can the guidance include or link to the risk of recurrence	Thank you for your comment. This has been added to the 'Terms used in the guideline' section, and included below the prescribing table (table 1). A link has been added.
158	NHS England and NHS Improvement South West	Guideline	3	1.1.5	Non- severe C.difficile infection does not necessarily need antibiotic treatment – for example if diarrhoea stops once the patient's antibiotics are stopped.	Thank you for your comment. The committee agreed that antibiotic treatment should be started when a diagnosis of *C. difficile* infection of any severity is suspected or confirmed. The committee discussed that in some people, symptoms may resolve without treatment but agreed

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						there is no way of identifying who these would be. Following discussion, they agreed that for people in the community, prescribers should consider seeking prompt specialist advice from a microbiologist or infectious diseases specialist before starting treatment, and this has been added to the recommendation. If subsequent stool sample tests to not confirm *C. difficile* infection, stopping these antibiotics should be considered.
159	NHS England and NHS Improvement South West	Guideline	3	11	Availability of FMT needs explaining – e.g. centres that produce FMT detailed for reference as an appendix	Thank you for your comment. Implementation issues are outside the scope of the guideline. Health organisations will need to ensure that faecal microbiota transplant is available in appropriate centres for a recurrent episode of *C. difficile* infection in adults who have had 2 or more previous episodes. Also see NICE's interventional procedure guidance on faecal microbiota transplant for recurrent *C. difficile* infection for further guidance.
160	NHS England and NHS Improvement South West	Guideline	3	11	Faecal transplant is a good option for patients with multiple recurrences but needs input of gastroenterologists and the system set up for its administration (typically in an acute hospital) and monitoring. WHC may occasionally have patients in whom this would be appropriate and referral route should be identified	Thank you for your comment. A recommendation has been added to ensure people in hospital with suspected or confirmed *C. difficile* infection have care from a multidisciplinary team that includes a microbiologist or infectious diseases specialist, gastroenterologist, surgeon, pharmacist and dietitian, as needed.

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						The committee recognised that there are some implementation challenges for this guideline. Local health organisations, health and social care practitioners and other stakeholders will need to work collaboratively to ensure that appropriate treatment is available for people with *C. difficile* infection. NICE are working with other national stakeholders such as NHS England and Improvement (including procurement teams) to support implementation of the guideline.
161	NHS England and NHS Improvement South West	Guideline	3	14	Suggest including the link to NICE MIB247 Faecal microbiota transplant for recurrent or refractory Clostridioides difficile infection Medtech innovation briefing [MIB247] Published date: 02 February 2021	Thank you for your comment. The Medtech innovation briefing on Faecal microbiota transplant for recurrent or refractory Clostridioides difficile infection is not formal NICE guidance. This will be stood down when this NICE guideline is published.
162	NHS England and NHS Improvement South West	Guideline Visual summary	4	1.1.10	It would be helpful to include in the guideline and visual summary more detail re advice to patients: if symptoms worsen rapidly. What symptoms and what is rapidly?	Thank you for your comment. The committee was not able to give more specific details on the advice to patients as this will depend on individual factors (for example, the type of symptoms experienced at presentation and their severity). This should be based on clinical judgement.
163	NHS England and NHS Improvement South West	Guideline Visual summary	4	1.1.10	It would be helpful to advise: healthcare workforce alert primary care that a person has/ had a CDI and be alert to future antibiotic prescribing that can increase risk of a recurrent CDI	Thank you for your comment. The committee discussed and agreed this was important and a new recommendation has been added to ensure that a diagnosis of *C. difficile* infection is recorded.
164	NHS England and NHS	Guideline Visual summary	4	1.1.11	It would be useful to specify what needs reassessment during antibiotic therapy and what the action should be. In the visual	Thank you for your comment. The actions related to antibiotic treatment are stated in the guideline:

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	Improvement South West				summary especially. Is this just an action to consider stopping antibiotic prescription for CDI due to stool sample test results then make it more clear this is the only action the statement relates to. Deterioration is covered in the blue H box	• If antibiotics have been started for suspected *C. difficile* infection, and subsequent stool sample tests do not confirm *C. difficile* infection, stopping these antibiotics should be considered. • If first line antibiotic treatment is ineffective, an alternative antibiotic is recommended (table 1). This has also been clarified in the prescribing table (table 1) which states 'Use clinical judgement to determine whether antibiotic treatment for C. difficile infection is ineffective. It is not usually possible to determine this until day 7 because diarrhoea may take 1 to 2 weeks to resolve'. The recommendation on reassessment has been amended to remove the 3 to 5 day time period. Other than the actions related to antibiotic treatment, the committee was not able to give more specific details about the assessment or reassessment as this will depend on individual patient factors. Further information (for example on stool sample tests) is available in Public Health England's guidance on diagnosis and reporting, and this is signposted in the recommendations on reassessment.
165	NHS England and NHS Improvement South West	Guideline Visual Summary	5 14	1 Table 1 30-32	Do pregnant women require referral and/or specialist advice? Consider including pregnant women in the visual summary maybe in the title content if	Thank you for your comment. From their experience, the committee agreed that it was very uncommon for a woman who is pregnant to present with *C. difficile*

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					pregnant women are treated in the same way as adults. This reduces uncertainty. Page 14 30-32 content is not helpful in terms of how to treat pregnant women	infection. If the clinician considers them to be at high risk of complications or recurrence, then referral can be considered. Furthermore, following discussion, the committee agreed that for people in the community, prescribers should consider seeking prompt specialist advice from a microbiologist or infectious diseases specialist before starting treatment, and this has been added to the recommendation. In the prescribing table (table 1), users are directed to the BNF for more information on appropriate use and dosing in specific populations (for example, hepatic impairment, renal impairment, pregnancy and breastfeeding). Information is also given on the use of vancomycin and fidaxomicin in pregnancy in the 'Medicines safety' section of the guideline.
166	NHS England and NHS Improvement South West	Guideline	5	19	Timely access to oral vancomycin and fidaxomicin in out of acute hospital care is a concern, especially in primary care settings. Access to oral liquid vancomycin formulations is a current challenge for hospitals, and use of powder for injection is unlikely to be easily accessed in a suitable form for safe administration in primary care settings. There are also limited licensed vancomycin powder for injection and oral use products in use and use of these to deliver via the oral route is a medication safety concern as a syringe for injection is required for reconstitution and	Thank you for your comment. The committee recognised that there are some implementation challenges for this guideline. Local health organisations, health and social care practitioners and other stakeholders will need to work collaboratively to ensure that appropriate treatment is available for people with suspected or confirmed *C. difficile* infection. NICE are working with other national stakeholders such as NHS England and Improvement (including

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					withdrawal; this risk can be minimised by pharmacy extemporaneous preparation in hospital settings, but is unlikely to be feasible in out of hospital settings. There is currently no UK licensed oral solution formulation of fidaxomicin.	procurement teams) to support implementation of the guideline. From their experience, the committee agreed that the number of people treated in the community for *C. difficile* infection who are also unable to take oral medicines (vancomycin capsules) is likely to be extremely small. The committee recognised the potential for medication errors when vancomycin powder for solution is reconstituted for oral or enteral administration. They agreed that vancomycin capsules are the preferred formulation to give vancomycin orally. They were aware that vancomycin powder for solution is also licensed to be given orally for *C. difficile* infection, and this is used in some settings (particularly if people cannot take solid oral medicines). However, they discussed that locally agreed protocols should be in place to reduce the risk of medication errors around reconstitution and administration, and to take account of the practicalities of administration, particularly in community settings. In response to stakeholder concerns, the committee have made the following changes to the recommendations: • Table 1 includes the oral dosage for vancomycin but no longer states the

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						dosage form (capsules or reconstituted powder for solution given orally). • A recommendation was added that for people who cannot take oral medicines, specialist advice should be sought from a gastroenterologist or pharmacist about alternative enteral routes for antibiotics. NICE are working with other national stakeholders such as NHS England and Improvement (including procurement teams) to support implementation of the guideline. The committee recognised that rarely, hospital admission may be required to ensure safe and appropriate administration. For people that need treatment with fidaxomicin and are unable to take tablets, the committee were aware that fidaxomicin granules for oral suspension have a current UK marketing authorisation and should be available in the UK (without the need to import) within 6 months of the publication of this guideline.
167	NHS England and NHS Improvement South West	Guideline	5	19	Table 1: Second line treatment is Fidaxomicin. This recommendation will be a challenging change in practice because there will be major cost implications here as it is £1200 a course.	Thank you for your comment. The committee noted the higher price of fidaxomicin, but they also noted the evidence that it was associated with lower rates of relapse/recurrence. Given the results of the economic modelling

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						undertaken comparing fidaxomicin to other second-line options, the committee were confident that the use of fidaxomicin would be cost-effective in this population. The committee also hope the cost-effectiveness work done for this guideline will help to encourage groups to make fidaxomicin available in those situations where it is clinically appropriate.
168	NHS England and NHS Improvement South West	Guideline	5	19	Table 1: The Microbiology team would agree that to exclude Metronidazole from first line treatment would not be significant factor and agree that vancomycin is first line	Thank you for your comment and your support for this recommendation.
169	NHS England and NHS Improvement South West	Guideline	5	19	Table 1: Microbiologists had anticipated that oral metronidazole would probably be dropped as standard first-line treatment for "mild" C.difficile disease and that oral vancomycin would be the standard (at a dose of 125mg qds). I think some microbiologists have concern regarding the duration of oral vancomycin therapy being 10 rather than 14 days, particularly for moderate or more severe infections and would generally suggest the longer duration. Some microbiologists also recommend a larger dose of 250mg or even 500mg but the evidence for this is poor and I don't have a problem with not seeing this in the guideline - for difficult cases there would be discussion with medical microbiologists in any event rather than depending entirely on the guideline.	Thank you for your comment. The randomised trials included in the clinical evidence based for this guideline all used a 10 day rather than 14 day dosing schedule, and therefore the committee agreed this was the one it would be appropriate to recommend. As you say, there will always be specific patients who have to be treated differently than the 'average' patients recruited in trials and considered in guidelines, as a result of their particular circumstances, and this would rely on appropriate judgement from the treating clinicians.
170	NHS England and NHS	Guideline	5	19	Table 1: Removal of metronidazole for treatment of mild to moderate C. difficile infection is very sensible.	Thank you for your comment and your support for this recommendation.

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171	NHS England and NHS Improvement South West	Guideline Visual Summary	6	Table 1	The Table refers to second-line antibiotic if vancomycin is ineffective; it would be helpful to include a definition of ineffective	Thank you for your comment. This has been clarified in the prescribing table (table 1) which states 'Use clinical judgement to determine whether antibiotic treatment for C. difficile infection is ineffective. It is not usually possible to determine this until day 7 because diarrhoea may take 1 to 2 weeks to resolve'.
172	NHS England and NHS Improvement South West	Guideline	6	Table 1	Fidaxomicin is expensive and only marginally better than vancomycin so advising as second-line in vancomycin failures or in repeated relapses seems reasonable	Thank you for your comment and your support for this recommendation.
173	NHS England and NHS Improvement South West	Guideline Evidence review	5	11-19	The antibiotic recommendation relies heavily on a single systematic review and network meta-analysis (Beinortas et al 2018) which includes 4 RCTs evaluating vancomycin vs fidaxomicin. Of these four, one compares a pulsed 25 day regimen of fidaxomicin vs standard regimen vancomycin – this should be excluded from the evidence on standard regimen fidaxomicin and the risk of recurrent C.diff. Of the 3 remaining RCTs none shows superiority over vancomycin, and only one shows a significant benefit of fidaxomicin for recurrence but only in the 027 ribotype, which now forms a very minor component of the UK burden of disease. I believe that the guideline is too proscriptive for the use of fidaxomicin, based on an incorrect interpretation of the available data, and that it should read that fidaxomicin should be considered as an alternative to	Thank you for your comment. The committee agreed the 25 day fidaxomicin regimen reflected a different treatment option, and in the network meta-analysis used to inform the cost-effectiveness modelling (see appendix L of the evidence review) this was kept sperate, with 'standard dose' and 'extended-dose' fidaxomicin being treated as different options. With no significant differences being found between these, the committee agree it was appropriate in recommendations to refer to the licensed 'standard-dose'. Once the remaining studies comparing fidaxomicin and vancomycin were pooled and the results used in the cost-effectiveness modelling undertaken, the committee agreed that vancomycin was

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					vancomycin, especially in association with the 027 ribotype.	the most cost-effective first-line option, with fidaxomicin being suitable second-line or in case of relapse. This reflects the position included in the recommendations in the guideline.
174	NHS England and NHS Improvement South West	Guideline	6	4-7	Small amount of evidence for the use of probiotics recommend should not be used routinely as number needed to treat is high. However there is evidence of the use of Lactobacillus rhamnosus in children with previous C.difficile in their stool to treat persistent diarrhoea.	Thank you for your comment. The committee agreed that there is some evidence (with many limitations) of a small effect with probiotics in preventing *C. difficile* infection. The single RCT data is very limited by the small sample size (n=14), which was a subgroup of a larger study in a subcontinental childhood population which is not necessarily generalisable to the UK setting. Because of concerns about the evidence base, the committee could not identify any scenario when the use of probiotics could be recommended in people taking antibiotics. Following stakeholder consultation, the recommendation has been amended so that it focuses on the advice given to people and states 'Do not advise people taking antibiotics to take prebiotics or probiotics to prevent *C. difficile* infection'.
175	NHS England and NHS Improvement South West	Visual Summary			The two page document was a good summary of the draft guidance and envisage this to be a useful source of information once the guidance is finalised	Thank you for your comment to support the use of the visual summary.
176	NHS England and NHS Improvement South West	Guideline	6	1.3	Any evidence on use of pre/pro biotics to reduce risk of recurrent CDI in at risk people where (antibiotics are excluded)?	Thank you for your comment. No prevention or treatment studies examined the incidence of recurrence of infection in

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						'at risk' populations for whom antibiotics were not used.
177	NHS England and NHS Improvement South West	Guideline	7 15 16	1 25-31 1-5	Terms used in the guidance: it would be useful to include the definitions of relapse and recurrent CDI here I note that content p15 lines 25-31 and p16 lines 1-5 refer to uncertainty with definitions and that defining relapse or recurrence is outside of the remit of the committee. However antibiotic treatment choices have been based on these definitions.	Thank you for your comment. This has been added to the 'Terms used in the guideline' section, and included below the prescribing table (table 1).
178	NHS England and NHS Improvement South West	Guideline	7	21	Recommendations for research: propose include an evaluation of the impact of implementation of these guidelines to inform future review in particular the issues discussed in page 14 lines 10-24	Thank you for your comment. The committee recognised that there are some implementation challenges for this guideline. Local health organisations, health and social care practitioners and other stakeholders will need to work collaboratively to ensure that appropriate treatment is available for people with suspected or confirmed *C. difficile* infection. NICE are working with other national stakeholders such as NHS England and Improvement (including procurement teams) to support implementation of the guideline.
179	NHS England and NHS Improvement South West	Guideline	7		Recommendations for research: There has been a sustained increase in the use of PPIs in older people aligned to the NHS medication safety programme. How has this impacted on the occurrence of CDI which PHE have reported has increased in FY 2019/20.	Thank you for your comment. Identifying risk factors for developing *C. difficile* infection is outside the scope of this guideline.
180	NHS England and NHS	Guideline	17	4	Might it be cost effective to treat first ever CDI with fidaxomicin in care home settings where	Thank you for your comment. No evidence was available for these specific

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	Improvement South West				IPC resources are less robust, and transmission has a higher impact due to the high risk population in residence?	circumstances or groups of patients, and in the absence of such evidence the committee did not feel confident in making different recommendations for this group to that made for the overall population.
181	NHS England and NHS Improvement South West	Economic model	1	13	Was cost to the patient included in the model? CDI was reported in the expert testimony as a 'straw that breaks the camel's back' leading to premature death in frail elderly patients. The opportunity to avid CDI may be valued more highly by this population, and their families. It is helpful to include an economic model in the guidance content	Thank you for your comment. NICE's methods state that we do not routinely include costs to patients in our analyses (either direct costs or time off work), and therefore this was not included. However, we agree this is likely to be an important factor, as it is in many other clinical conditions, and would therefore provide additional weight to decisions such as moving away from using metronidazole to options that are likely to have higher cure rates and lower rates of recurrence.
182	Royal College of Paediatrics and Child Health	Guideline	General	General	Clostridioides Difficile being a hyper virulent organism causing serious epidemiological problems, the biggest impact on practice will be in the areas of prevention, proper diagnosis and effective treatment.	Thank you for your comment. NICE are working with other national stakeholders such as NHS England and Improvement (including procurement teams) to support implementation of the guideline, and your responses will help to inform that work.
183	Royal College of Paediatrics and Child Health	Guideline	General	General	Please keep in mind that currently there is no consensus in the best method for detecting CDI, almost every antibiotic used can be a risk for CDI, even the drugs used to treat CDI such as Vancomycin or Metronidazole. Emphasis should be more on the preventive aspects especially in those with co-morbidities and risk factors.	Thank you for your comment. Diagnosis of *C. difficile* infection is outside the scope of this guideline. Users are signposted to Public Health England's guidance on diagnosis and reporting. Infection control procedures and antimicrobial stewardship is also outside the scope of this guideline. However, the guideline now signposts to other relevant national guidance in the 'Preventing *C. difficile* infection' section, which cover

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						these aspects – Public Health England's guidance on *C. difficile* infection: how to deal with the problem, NICE's guidance on healthcare-associated infections and NICE's guidance on antimicrobial stewardship.
184	Royal College of Paediatrics and Child Health	Guideline	General	General	Recommendation statements, in general, have been discussed taking into consideration the scientific evidence for its formulation – in particular covering the relationships between the guidelines and scientific data This should translate into high acceptance level by experts.	Thank you for your comment.
185	Royal College of Paediatrics and Child Health	Guideline	General	General	Key issues or learning points for professional groups: • Assess the severity of initial infection, subsequent likelihood of cure, recurrence, mortality and outcomes of subsequent recurrences. • Differentiate between recurrence and re-infection and identify carriers • Recognise the high prevalence of asymptomatic colonization in younger children • Adopt preventive measures for fecal-oral spread, normal intestinal flora disruption and employ cautious use of probiotics • Fidaxomycin – to be cost effective over vancomycin for initial CDI therapy due to decreased risk of recurrence and subsequent hospitalisation. Further research is required in this regard • Proper antibiotic stewardship	Thank you for your comment. NICE are working with other national stakeholders such as NHS England and Improvement (including procurement teams) to support implementation of the guideline, and your responses will help to inform that work.

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					• Monoclonal antibodies and vaccines represent a future perspective against CDI.	
186	Royal College of Paediatrics and Child Health	Guideline	General	General	The reviewer is happy with this guideline.	Thank you for your comment.
187	NHS England and NHS Improvement	Evidence review	General	General	The evidence does not determine what clinicians should do if antibiotic treatment and FMT both fail. This could be an early indicator of emerging resistance of C.diff to antibiotic treatment (RM)	Thank you for your comment. The committee discussed that the scenario described was likely to be a rare occurrence, and specialist advice would be sought.
188	NHS England and NHS Improvement	Guideline	2	4	Consideration needs to be given to those with cognitive impairments and how they will be supported to understand the condition and maintain their wellbeing and the safety of others. Also consideration should be given to children and their unique needs. Suggest more detail here as to best practice for IPC, providing advice and support of others and other services to ensure individuals' engagement is maximised. (NP)	Thank you for your comment. The guideline population is all people aged 72 hours and over. The guideline recommendations are presented as a visual summary as well as in the guideline, which are written in language that is simple and straightforward. There are options for prescribing which have different dose regimens which may be suitable for people who may need simplified regimens. The points raised in relation to specific patient groups are important considerations when they are receiving any care and are not specific to treating *C. difficile* infection. Further implementation issues around supporting people with cognitive impairment to understand their condition is outside the scope of this guideline. See also the NICE guideline on Decision-making and mental capacity.

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189	NHS England and NHS Improvement	Guideline	5	1	Suggest again this needs further information to support clinicians to understand the best practice steps here. Mental capacity or age of the individual, language barriers and/or other associated conditions may need further attention therefore "refer into" is too simplistic. (NP)	Thank you for your comment. The guideline population is all people aged 72 hours and over. The guideline recommendations are presented as a visual summary as well as in the guideline, which are written in language that is simple and straightforward. There are options for prescribing which have different dose regimens which may be suitable for people who may need simplified regimens. The points raised in relation to specific patient groups are important considerations when they are receiving any care and are not specific to treating *C. difficile* infection. Further implementation issues around supporting clinicians to communicate effectively with people with cognitive impairment or language barriers is outside the scope of this guideline. See also the NICE guideline on Decision-making and mental capacity.
190	NHS England and NHS Improvement	Guideline	5	11	Reiterate the need for further detail as to how to effectively communicate the treatment with the person and/or their carers. Antibiotics may have a number of side effects the person will need to be aware of and may have specific methods of administration which again will need to be clear and supported in practice. (NP)	Thank you for your comment. The guideline population is all people aged 72 hours and over. The guideline recommendations are presented as a visual summary as well as in the guideline, which are written in language that is simple and straightforward. There are options for prescribing which have different dose regimens which may be suitable for people who may need simplified regimens.

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						Further implementation issues around supporting clinicians to communicate effectively with people with cognitive impairment or language barriers is outside the scope of this guideline. See also the NICE webpage on making decisions about your care.
191	NHS England and NHS Improvement	Guideline	6	3	Suggest further detail explaining what the clinician should do and not just *not do*. So explaining to people the use of antibiotics, exploring the reason for the request, outlining the risks associated with over use of antibiotics. (NP)	Thank you for your comment. Recommendations are given in the guideline explaining what the clinician should do as well as not do. Antimicrobial stewardship is outside the scope of this guideline. However, the guideline now signposts to other relevant national guidance in the 'Preventing *C. difficile* infection' section, which cover these aspects – Public Health England's guidance on *C. difficile* infection: how to deal with the problem, NICE's guidance on healthcare-associated infections and NICE's guidance on antimicrobial stewardship.