UK Health Security Agency

Clostridioides difficile infection

Updated guidance on management and treatment

Contents

Executive summary 3
1. Evidence base for recommended management and treatment of CDI 4
Infection prevention and control 4
Diagnosis and assessment of CDI 5
Supportive care 6
Treatment for a first episode of CDI (non-severe or severe) 7
Treatment for life-threatening CDI 8
Treatment for recurrent CDI 8
Treatment of CDI in children and young people under 18 9
Access to specialist advice 9
2. Evidence base for alternative agents 10
Faecal microbiota transplantation (FMT) 10
Bezlotoxumab 11
Intravenous immunoglobulin (IVIG) 11
Prebiotics 11
Probiotics 12
Rifaximin 12
Other agents 12
3. Recommendations 13
Infection prevention and control 13
Management of suspected cases of CDI 13
All medications should be reviewed 14
Assess severity of CDI (at baseline and daily) 14
Supportive care and clinical review 14
Treatment for a first episode of non-severe or severe CDI 15
Treatment for life-threatening CDI 15
Treatment for recurrent CDI 16
Treatment for more than 2 episodes of CDI 16
Post-infectious irritable bowel syndrome (PI-IBS) 16
Prebiotics and probiotics are not recommended for the treatment or prevention of CDI 16
4. Treatment algorithm 17
Appendix 1. Start Smart Then Focus antimicrobial stewardship algorithm 21
Appendix 2. Interpretation of a 2-step *C. difficile* testing algorithm 23
Appendix 3. The Bristol stool chart 24
Appendix 4. Acknowledgements 25
References 26

Executive summary

Clostridioides difficile infection (CDI) is estimated to cause 20 to 30% of antibiotic-associated diarrhoea (1). In the UK, the annual incidence of CDI was 22.2 per 100,000 population between April 2020 and March 2021 and this figure has been relatively stable since 2013 (2). It carries considerable risk of morbidity and 30-day all-cause mortality is estimated to be between 9 and 38% (3). Since its recognition as a significant healthcare associated infection, multiple infection control measures and treatment modalities have been explored and this remains an evolving field. Crucially, the management of severe CDI should considered a medical emergency and urgently assessed and then reviewed regularly, preferably by a multidisciplinary team, to ensure that patients receive prompt and optimised care.

This document is an update of the guidance on the management of CDI published in 2013 and replaces the previous version. The National Institute for Health and Care Excellence (NICE) have recently published updated guidelines on antimicrobial prescribing for CDI in adults, children and young people following a review of the evidence for all antibiotics available in the UK, based on a network meta-analysis and cost-effectiveness modelling (4, 5, 6). The following guidance has been broadly aligned with NICE recommendations and agreed by a small expert sub-group (Appendix 4) following an independent literature review. NICE recommendations do not cover non-antimicrobial therapeutics such as faecal microbiota transplantation (FMT) and advice relating to diagnostic criteria, severity assessment, infection prevention and control (IPC measures) and unlicenced use of antimicrobials, This guidance provides recommendations based on expert opinion supported by the NICE evidence review and subsequent literature review for the assessment and management of patients with suspected or confirmed CDI.

1. Evidence base for recommended management and treatment of CDI

Infection prevention and control

1.1 Antibiotic exposure almost always precedes *Clostridioides difficile* infection (CDI) (7). At least 20% of antibiotics prescribed in primary care were unnecessary, therefore antimicrobial stewardship programmes (ASP) are priority interventions in the control of this healthcare-associated infection (HCAI) (8). Although establishing a causal link between interventions such as ASP and CDI is challenging, there is increasing evidence for their efficacy (9, 10). A recent meta-analysis by Baur and others of 32 trials reported a 32% reduction in incidence of CDI associated with ASP (IR 0.68, 95% CI 0.53 to 0.88, p=0.0029) (10). For further information, please refer to NICE guidance on antimicrobial stewardship and the PHE 'Start Smart then Focus' toolkit (11, 12, 13).

1.2 Appropriate and timely infection control measures are key prevention strategies, including barrier nursing of hospitalised patients in a side room with en-suite facilities (if available), hand washing with soap and water (because alcohol-based hand rub is not effective at removing *C. difficile* spores), use of appropriate Personal Protective Equipment (PPE) (gloves and apron), and effective decontamination of patient equipment and environmental surfaces with daily and terminal cleaning. Decontamination with hydrogen peroxide after use of a sporicidal cleaning agent has been shown to be highly effective for removing residual environmental C. diffcile spores (14). It has also been associated with reduced incidence of hospital-acquired CDI compared to other decontamination methods (15). Further guidance and a more detailed discussion of the evidence for infection control measures for *C. difficile* can be found in guidance produced by Department of Health (DoH), National Institute for Clinical Excellence (NICE) and European society of clinical microbiology and infectious diseases (ESCMID) Study Group for *C. difficile* (ESGCD) (16, 17, 18, 19).

1.3 Ribotyping of isolates is sometimes useful in the investigation and control of suspected outbreaks. In England, the *C. difficile* ribotyping network (CDRN) has been established since 2007 and is now PCR-based. Individual trusts can send isolates for typing to the national reference centre in Leeds (20, 21). Although CDI due to certain ribotypes (for example, RT027, RT 078, and RT220) has been associated with increased severity, recurrence and mortality, clinical trials have found no robust evidence for difference in clinical efficacy between antibiotic agents according to ribotype (22 to 27). Routine ribotyping is therefore not recommended and ribotype should not influence clinical treatment decisions.

Diagnosis and assessment of CDI

1.4 The diagnosis of CDI is based on a combination of clinical and laboratory findings. It is defined by the presence of diarrhoea with the detection of either *C. difficile* toxins or toxigenic *C. difficile* in stool. However, there are inherent diagnostic uncertainties around the significance of the detection of the bacterium or toxin genes, in contrast to the detection of toxin in stool (28, 29). Toxin testing by enzyme immunoassay (EIA) alone is unsuitable due to limited specificity. A 2-step testing system is recommended as follows: step 1) a highly sensitive screening test (GDH EIA, NAAT or PCR) with positive samples proceeding to step 2) highly specific testing with toxin A/B EIA (28, 30). A clinical diagnosis of CDI can be made in the presence of pseudomembranous colitis detected endoscopically or on histopathology samples.

1.5 There are no definitive markers of severity, and a severity score is needed that is validated in more than one setting. Our previous guidance published in 2013 recommended the use of 4 categories of severity: mild, moderate, severe and life-threatening. However, in line with current NICE evidence review and 2017 Infectious Disease Society America guidelines, CDI is now classified as non-severe, severe and life-threatening (or 'fulminant') infection (5, 6, 29).

1.6 The 3 most frequently recognised risk factors for severe CDI are age, peak leukocytosis and blood creatinine (25, 31 to 33). However, age is non-specific, and no single parameter is strongly predictive of severe CDI, with the possible exception of very high white cell count (WCC). Elevated blood lactate greater than 5 mmol/L is associated with extremely poor prognosis, even with colectomy (34). We recommend a conservative WCC threshold of more than $15x10^9$/L, due to immunesenescence that is common in elderly patients. Disease severity based only on the number of diarrhoeal stools may be limited by difficulties in accurately recording the numbers of stool in patients (noting issues such as varying faecal volumes and faecal incontinence) and because some cases of severe CDI are characterised by ileus with no diarrhoea.

1.7 Approximately 25% of patients experience a further episode or 'recurrence' of CDI after initial treatment with metronidazole or vancomycin (25, 26). The risk of recurrence increases with each subsequent episode – 40% of those with a second episode go on to have a third, and 5 to 60% of individuals with a third episode go on to have 4 or more episodes (31, 35, 36). 'Relapse' occurs early after symptom resolution and is more likely to be with the same strain of *C. difficile*. 'Re-infection' generally occurs at a later time point and is more likely to be due to a different strain (37, 38). Factors associated with increased risk of CDI recurrence include age over 65 years, female gender, raised leucocyte count, multiple co-morbidities, length of hospital admission, nursing home residence, and continued use of antibiotics for non-CDI indications (39, 40, 41).

1.8 Although tests for *C. difficile* (free) toxin assays may remain positive for 28 days after the start of treatment, *C. difficile* toxin assays become negative in 90% of cases by day 5 (33). If a patient has recurrent syptoms, repeat tesing is indicated, noting that post-infectious irritable bowel syndrome can occur and so a clinical diagnosis of recurrent CDI may be inaccurate.

1.9 Post-infectious irritable bowel syndrome (PI-IBS) has been estimated to affect 21.5% of patient following CDI (95% CI 8.2% to 35.7%) (42). However, this estimate is based on a meta-analysis of 15 studies with a number of methodological issues, and this remains an understudied area. Diagnosis of PI-IBS is based on fulfilment of the Rome IV criteria for IBS with onset following an episode of acute infectious gastroenteritis (43). It has been suggested that PI-IBS results from gut dysbiosis and Faecal Microbial Transplant (FMT) has been trialled in PI-IBS with mixed results (44). See section 2.8 for further discussion of the evidence for FMT in CDI.

1.10 Routine culture and antimicrobial sensitivity testing of *C. difficile* isolates is not used because it is technically difficult. A meta-analysis of 53 studies found that the weighted pooled prevalence resistance of isolates to vancomycin increased from 1.9% in the period 1982 to 2012 to 2.3% in studies 2012 to 2019 (45). The ClosER study monitored antimicrobial susceptibility and geographical distribution of *C. difficile* ribotype from 2011 to 2016 in 28 European countries (3,499 isolates from 40 sites) (46). Ribotype diversity scores for each country were calculated and mean MIC results used to generate cumulative resistant scores (CRSs) for each isolate and country. The fidaxomicin geometric mean MIC for years one to 5 was 0.04 mg/L. Only one fidaxomicin-resistant isolate (RT344) was submitted (MIC greater than or equal to 4 mg/L). Metronidazole and vancomycin geometric mean MICs were 0.46 mg/L and 0.75 mg/L, respectively. Of prevalent ribotypes, 027, 017 and 012 demonstrated resistance or reduced susceptibility to multiple antimicrobials. Ribotype diversity was inversely correlated with mean CRS for individual countries (Pearson coefficient r = − 0.57). Overall, *C. difficile* RT prevalence remained stable in 2011 to 2016. To date fidaxomicin resistance has only been described in one isolate worldwide (47, 48). However, reference laboratories carry out periodic surveillance to monitor for the development of antimicrobial resistance in *C. difficile* in the face of changing epidemiology and selection pressures (49).

Supportive care

1.11 Previous reports have highlighted the important role of supportive care that include a need for multidisciplinary assessment of patients prone to electrolyte imbalance, dehydration, malnutrition and pressure sores (50). Medication that might exacerbate diarrhoea or exacerbate intra-vascular fluid depletion or kidney injury should be reviewed. This includes stopping laxatives, and reviewing non-steroidal anti-inflammatories (NSAIDs), ACE-inhibitors and diuretics. Please see NICE advice on supportive care in gastroenteritis in adults and children (51, 52).

1.12 The precipitating antibiotic should be stopped wherever possible: agents with less risk of inducing CDI can be substituted if an underlying infection still requires treatment (53, 54). Where concomitant antibiotics are essential for another infection, consideration should be given to the use of fidaxomicin in preference to vancomycin for the treatment of CDI. This issue was not addressed in the latest NICE guidance. However, evidence for this comes from sub-group analyses of a pair of head to head trials demonstrating non-inferiority of fidaxomicin to vancomycin for cure of CDI and superiority for recurrence of CDI (26, 55). Cornely and colleagues found a significantly higher cure rate with fidaxomicin than with vancomycin in patients receiving concomitant antibiotics (90.2% and 73.3% respectively, p=0.031).

1.13 There is a risk that antimotility agents (such as loperamide) could precipitate toxic megacolon by slowing the clearance of *C. difficile* toxins from the intestine. There is evidence of poor outcomes in CDI patients who received anti-motility agents. However, reviews of case reports and series suggest that most of these patients did not receive specific treatment for CDI (56, 57). No randomised trials are available. Avoidance of anti-motility agents in acute infection is recommended.

1.14 Proton pump inhibitors (PPIs) have been associated with CDI risk, although studies to date have been observational with risk of residual confounding (patients with multiple co-morbidities are more likely to be prescribed PPI and more likely to develop CDI) (58). No causal link has been made and there is no evidence from systematic reviews or randomised controlled trials that stopping PPIs in patients with CDI leads to improved outcomes (59). However, given that PPIs, may be over prescribed and not frequently reviewed, consideration should be given to stopping/reviewing the need for PPIs in patients with/at high risk of CDI.

Treatment for a first episode of CDI (non-severe or severe)

1.15 A recent Cochrane review and meta-analysis reported no significant difference in symptomatic cure with low versus high dose vancomycin (125mg QDS versus 500mg QDS) (60). When oral administration is not possible or will not reach the colon (for example, in patients with Hartman's pouch, ileostomy and so on), vancomycin can be administered via a rectal enema (61) possibly in addition to intravenous metronidazole. A recent systematic review and random-effects network meta-analysis (NMA) of 24 RCTs compared antibiotic treatments for a first episode or first recurrence of CDI in adults (4). The following studies were excluded: published before 2000, had less than 50 participants per arm, or were unblinded. Fidaxomicin was the highest-ranking treatment available in the UK, followed by vancomycin. Metronidazole ranked last among available antibiotics (including teicoplanin, fidaxomicin, vancomycin, rifaximin and fusidic acid). The raw data from the Beinortas and colleagues NMA was used to inform the health economic modelling conducted in the recent NICE guidelines for antimicrobial prescribing for CDI. This modelling determined that

vancomycin was preferred on a cost basis as first-line antibiotic option regardless of severity or risk of recurrence (5, 6). An additional consideration comes from the EXTEND study which compared standard dosing of fidaxomicin (200mg BD for 10 days) with an extended dosing regimen (200mg BD for 5 days followed by 200mg OD on alternate days from day 7 to day 25) (62). The authors reported improved sustained response with the extended dosing regimen (2% versus 17% at day 40), however the study was unblinded and sample sizes in each sub-group were small. Therefore, further studies are needed before adoption into routine clinical practice. See section 2 for further discussion of the evidence for alternative agents for a first episode of CDI.

1.16 Symptoms of diarrhoea will only resolve in about 60% of cases by day 5 of therapy. Diarrhoea will resolve in a further 30% of cases by day 10, with a few cases resolving after day 10 despite no additional treatment (26). If the clinical condition of a patient is improving it is not necessary to alter therapy simply because symptoms have not resolved by 5 or even 10 days.

Treatment for life-threatening CDI

1.17 For patients with life-threatening CDI, seek specialist advice. The recent NICE evidence review supports consideration of oral vancomycin (500mg QDS for 10 days) + intravenous metronidazole (500mg TDS for 10 days) (5, 6). Fidaxomicin (200mg BD for 10 days) can also be considered, however this recommendation is based on expert opinion. In severe disease vancomycin can be given rectally via retention enema (61). See sections 2.3 and 2.7 for discussion of the evidence for FMT and IVIG in the context of life-threatening CDI, respectively.

1.18 Treatment for life-threatening CDI may include surgery and urgent surgical review is important. The World Society of Emergency Surgery have recently published updated guidelines for the management of CDI in surgical patients (63). Their recommendation stress the importance of early surgical review and recommend that resection of the entire colon be considered in patients with fulminant colitis. This is based on evidence from several systematic reviews reporting better outcomes in patients where surgery was performed before the onset of shock or the development of vasopressor requirement (64 to 67). Diverting loop ileostomy with colonic lavage is a colon-sparing alternative, and although studies comparing these techniques are limited in number and observational, outcomes appear to be similar (68 to 71).

Treatment for recurrent CDI

1.19 For patients with a recurrent episode of CDI 12 or more weeks after the resolution of symptoms, either oral vancomycin (125mg QDS for 10 days) or oral fidaxomicin (200mg BD for 10 days) are recommended (5, 6). A single centre open label RCT found no statistically significant difference in clinical effectiveness for recurrent CDI for vancomycin compared to

fidaxomicin at 5 weeks (72). Tapering or pulsed vancomycin may have a role in patients with refractory or recurrent CDI and there are ongoing studies in this area. In the recent evidence review conducted by NICE, its use was limited to studies in which it was co-administered with FMT and so such therapy was not recommended (6). US guidance continues to recommend the use of pulsed vancomycin for a first recurrence of CDI (36). See sections 2.4, 2.6 and 2.7 for further discussion of the evidence for the use of FMT, bezlotoxumab and IVIG in the context of recurrent CDI, respectively.

Treatment of CDI in children and young people under 18

1.20 As per the recent NICE guidelines (2021), we recommend that treatments should be provided or guided by a specialist (microbiologist, paediatric infectious diseases, paediatric gastroenterologist) (5). Oral antibiotics should be offered, with the choice of agent based on adult treatment recommendations with reference to licenced indications for children and adolescents (73).

Access to specialist advice

1.21 If access to or experience in use of therapeutic agents or treatments such as FMT is unavaible locally, specialist advice should be sought from appropriate regional centres.

2. Evidence base for alternative agents

Faecal microbiota transplantation (FMT)

2.1 Different methods have been used to infuse intestinal microorganisms into the intestines of patients with the aim of restoring the gut microbiome. Typically, fresh manipulated faeces (30–50g) from a healthy donor is administered in normal saline by enema, slurries via nasogastric tube, or colonoscopy. Standardisation of the delivery of FMT is still needed with debate over the selection and screening of donors, formulation and storage of material (fresh versus frozen), and route of administration (74, 75).

2.2 Faecal microbiota transplantation (FMT) is not recommended for the treatment of a first episode of CDI as there is no significant difference in clinical effectiveness when compared to vancomycin (76).

2.3 The role of FMT in fulminant or life-threatening CDI is uncertain and supported by low quality evidence. A recent systematic review concluded that there was low quality evidence to support it's use in this context and further research is warranted (77). Recent European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guidance suggests consideration of FMT as rescue therapy in fulminant CDI for patients who have deteriorated despite antibiotic treatment and for whom surgery is not feasible. However, the evidence supporting this recommendation was noted to be weak (78).

2.4 FMT is recommended in patients who have had 2 or more episodes of CDI (5, 6, 79). A systematic review concluded that this approach was highly effective at achieving resolution of recurrent CDI (92% resolved) and that adverse events were rarely reported (80). Two open label RCTs have since been reported which demonstrated clinical efficacy in patients with recurrent CDI (72, 81). The RCT conducted by van Nood and colleagues was stopped at interim analysis because of the high rate of recurrent CDI among participants in the vancomycin arms (31% resolution with 14 days of vancomycin alone versus 23% with 4 to 5 days vancomycin and bowel lavage, and 81% with 4 to 5 days of vancomycin followed by bowel lavage and FMT, p<0.001 for either vancomycin regimen compared with FMT). The RCT conducted by Hvas and colleagues found that 4 to 10 days of vancomycin followed by FMT was superior to both 10 days of fidaxomicin and 10 days of vancomycin using a combined outcome of symptom resolution and negative stool PCR at 8 weeks (71% in FMT arm versus 33% p= 0.009 and 19% p=0.001 respectively). Notably, a systematic review and meta-anaylsis involving 13 trials and 610 patients concluded that FMT was associated with lower clinical cure rates in RCTs than in open-label or observational studies (67.7% versus 82.7% respectively, p< 0.01) (82). This review also concluded that delivery of FMT by colonoscopy or oral routes (such as nasojejunal tubes) were more effective than by enema.

2.5 Cost and safety are important considerations with FMT. Each out-patient FMT treatment costs approximately €3,000 and there have been serious associated adverse events, including deaths, due to the transmission of pathogenic and/or multi-resistant organisms (83, 84, 85).

Bezlotoxumab

2.6 Bezlotoxumab is a human monoclonal antibody against *C. difficile* toxin B which has been trialled as an adjunct to antibiotics to prevent recurrent CDI. It was shown in a pair of RCTs (MODIFY I and MODIFY II) to have a significantly lower rate of recurrent CDI compared to placebo (17% versus 28%, adjusted difference -10.1 percentage points, 95% CI -15.9 to -4.3) with a safety profile similar to placebo (86). Although not recommended by NICE due to cost, bezlotoxumab can be used as an adjunct to antibiotics to prevent recurrent CDI with specialist input (5, 6).

Intravenous immunoglobulin (IVIG)

2.7 Intravenous immunoglobulin (IVIG) is pooled human serum that contains antibodies against *C. difficile* toxins A and B. However, the evidence to support it's use is limited. There have been a number of case reports and small case series reporting favourable outcomes in severe or refractory CDI (53, 87 to 92). One retrospective single group open label evaluation of the efficacy of different preparations of IVIG reported a clinical response in 10 out of 17 (59%) cases (93). Although no RCTs have evaluated the treatment or efficacy of IVIG, a single intravenous dose of 400mg/kg may be considered in severe or recurrent CDI (94).

Prebiotics

2.8 Prebiotics are not recommended for the treatment or prevention of CDI due to limited evidence. No systematic reviews of prebiotics for the treatment of CDI were included in the most recent NICE evidence review and network meta-analysis (5, 6).

2.9 There has been one RCT evaluating prebiotics as primary prevention of CDI in adults taking antibiotics (95). This did not find significant differences between groups randomised to receive 7 days of oligofructose compared to placebo in terms of incidence of diarrhoea overall, incidence of *C. difficile*-associated diarrhoea, length of hospital stay, or all-cause mortality. The same authors looked at prebiotics for secondary prevention of recurrent diarrhoea in adults in a double-blind RCT involving hospitalised adults over the age of 65 (96). Those who received 30 days of 12g per day of oligofructose had a lower rate of recurrent diarrhoea at 30 days follow up compared to placebo (8.3% versus 34.3%, <0.001). However, there was no significant difference in *C. difficile* culture positivity at 30 or 60 day follow-up. Due to limited evidence for efficacy prebiotics are not recommended for primary or secondary prevention of CDI.

Probiotics

2.10 No systematic reviews or meta-analyses met the inclusion criteria set-out by NICE, for the use of probiotics for the treatment of CDI in adults (6).

2.11 One study has demonstrated a benefit of probiotics in the treatment of children in India with CDI (97). In this RCT involving children with persistent diarrhoea for over 14 days, oral rehydration solution with *Lactobacillus rhamnosus* GG powder twice daily for 7 days was associated with decreased frequency and duration of diarrhoea and vomiting. The commonest pathogens identified in this study were *Escherichia coli* and *Shigella spp.*, with 14/90 (15%) positive for *C. difficile*. Among those with CDI there was low-quality evidence for a reduction in the number of days of diarrhoea in those who received *L. rhamnosus* GG. Another systematic review of 18 RCTs in children found that oral *Lactobacillus rhamnosus GG* was associated with a shorter duration in diarrhoea and shorter hospitalisation among in-patients (98). An RCT in adults aged over 65 years found no benefit from a multistrain preparation of lactobacilli and bifidobacteria in the prevention of antibiotic associated diarrhoea or CDI (99).

2.12 A recent multinational systematic review and meta-analysis examined the evidence for probiotics in the prevention of CDI in adults and children (100). A meta-analysis including 24 trials found moderate evidence that probiotics prevented CDI incidence when compared with placebo (1.37% versus 3.25%, RR 0.40, 95% CI 0.30-0.54, NNT 54). However, the incidence of CDI was not statistically significantly reduced across all sensitivity analyses.

Rifaximin

2.13 Rifaximin is an oral, non-absorbed rifamycin (related to rifampicin). There is limited evidence for the use of rifaximin in preventing further recurrences of CDI in people who have had previous recurrent infection (101). However, a recent RCT comparing 28 days of rifaximin to placebo in patients with a first or recurrent episode of CDI found no difference in recurrence rates (102). Additionally, the antibiotic regimens used raise concerns about the emergence of rifamycin resistance which has been reported in vivo in CDI (103, 104, 105). Neither rifaximin nor rifampicin is therefore recommended for the prevention of CDI recurrence.

Other agents

2.14 There is no robust evidence to support the use of alternative treatment agents including anion exchange resins (such as cholestyramine and tolevamer), non-toxigenic *C. difficile* (NCTD), rifampicin, fusidic acid and nitazoxanide. There is limited evidence to suggest a role for teicoplanin, as well as a lack of biological plausibity that it should be superior to vancomycin, and further research is warranted (5, 6).

3. Recommendations

Infection prevention and control

Antimicrobial stewardship programmes are a key intervention in the prevention of CDI. See Appendix 1 for the 'Start Smart then Focus' antimicrobial stewardship algorithm.

Hands must be washed with soap and water because alcohol-based hand rub is not effective at removing *C. difficile* spores.

Patients should be barrier nursed in side rooms with en-suite facilities (if available).

Gloves and aprons are the PPE that is required for routine care of patients with CDI.

Effective decontamination of patient equipment and environmental surfaces is an important component of control of *C. difficile* infection. Daily and terminal cleaning advised in the hospital setting. Decontamination with hydrogen peroxide after use of a sporicidal agent is recommended.

Routine ribotyping is not recommended.

Management of suspected cases of CDI

Clinicians (doctors and nurses) should apply the following mnemonic protocol (SIGHT) when managing suspected potentially infectious diarrhoea:

S	Suspect that a case may be infective where there is no clear alternative cause for diarrhoea
I	Isolate the patient and consult with the infection prevention and control (IPC) team while determining the cause of the diarrhoea
G	Gloves and aprons must be used for all contacts with the patient and their environment
H	Hand washing with soap and water should be carried out before and after each contact with the patient and the patient's environment
T	Test the stool using a 2-step testing system, sending a specimen immediately (see Appendix 2 for interpretation of a 2-step testing system)

All medications should be reviewed

Stop antibiotics that are not essential for a non-CDI indication.

Stop laxatives.

Review and consider stopping PPIs, diuretics, ACE-inhibitors and NSAIDs.

Assess severity of CDI (at baseline and daily)

Non-severe CDI	Associated with a raised WCC that is less than 15x10⁹/L. Typically associated with fewer than 5 stools of type 5 to 7 on the Bristol Stool Chart (see Appendix 3) per day.
Severe CDI	Associated with a WCC greater than 15x10⁹/L, or an acute rising serum creatinine (that is, greater than 50% increase above baseline), or a temperature of more than 38.5°C, or evidence of severe colitis (abdominal or radiological signs). The number of stools may be a less reliable indicator of severity.
Life-threatening CDI	Includes hypotension, partial or complete ileus or toxic megacolon, or computerised tomography (CT) evidence of severe disease such as fulminant colitis. Elevated blood lactate greater than 5mmol/L is a poor prognostic sign.

Supportive care and clinical review

CDI should be managed as a diagnosis in its own right, with each patient reviewed daily regarding fluid resuscitation, electrolyte replacement and nutrition review.

Patients should be monitored daily for frequency and severity of diarrhoea using the Bristol Stool Chart but please note that diarrhoea may take up to 1 to 2 weeks to resolve.

Monitor for signs of increasing severity of disease, with early referral to ITU and early surgical review as patients may deteriorate very rapidly.

Integrated Care Systems (ICSs) should ensure that trusts have a multidisciplinary clinical review team consisting of a microbiologist, an infectious diseases or infection prevention and control doctor, a gastroenterologist or surgeon, a pharmacist, a dietician, and an infection prevention and control nurse.

This multidisciplinary clinical review team should review all CDI patients at least weekly to ensure that the infection is being treated optimally and that the patient is receiving all necessary supportive care.

Treatment for a first episode of non-severe or severe CDI

(See section 4 for the treatment algorithm.)

First-line treatment – oral vancomycin 125mg QDS for 10 days.

Second-line treatment – oral fidaxomicin 200mg BD for 10 days.

Third-line treatment – seek specialist advice. Specialists may consider oral vancomycin up to 500mg QDS for 10 days +/- intravenous metronidazole 500mg TDS for 10 days. Fidaxomicin 200mg BD for 10 days may also be considered.

For patients with a first episode of CDI who require ongoing antibiotics for non-CDI indication: consider oral fidaxomicin 200mg BD for 10 days.

Please see Specialist Pharmacy Service guidance on choosing between oral vancomycin options and refer to the British National Formulary for considerations in patients who are pregnant, breastfeeding, or have renal or hepatic impairment (106, 107).

Treatment for life-threatening CDI

Seek specialist advice.

Oral vancomycin 500mg QDS for 10 days with intravenous metronidazole 500mg TDS for 10 days. If necessary, vancomycin can be administered via a nasogastric tube or rectally via retention enema. Fidaxomicin (200mg BD for 10 days) can also be considered.

Close clinical monitoring with early surgical and intensive care input are advised. Blood lactate should be measured. Colectomy should be considered, especially if caecal dilatation is more than 10cm.

The addition of intravenous immunoglobulin (IVIG) at a dose of 400 mg/kg may be considered with specialist input. FMT may also be considered in life-threatening CDI with specialist input.

Treatment for recurrent CDI

Within 12 weeks of symptom resolution – oral fidaxomicin 200mg BD for 10 days.

More than 12 weeks after symptom resolution – oral vancomycin 125mg QDS for 10 days OR oral fidaxomicin 200mg BD for 10 days.

Treatment for more than 2 episodes of CDI

Seek specialist advice to discuss.

Consider FMT in patients who have had 2 or more episodes of CDI, assuming that optimised licensed therapeutic options have already failed.

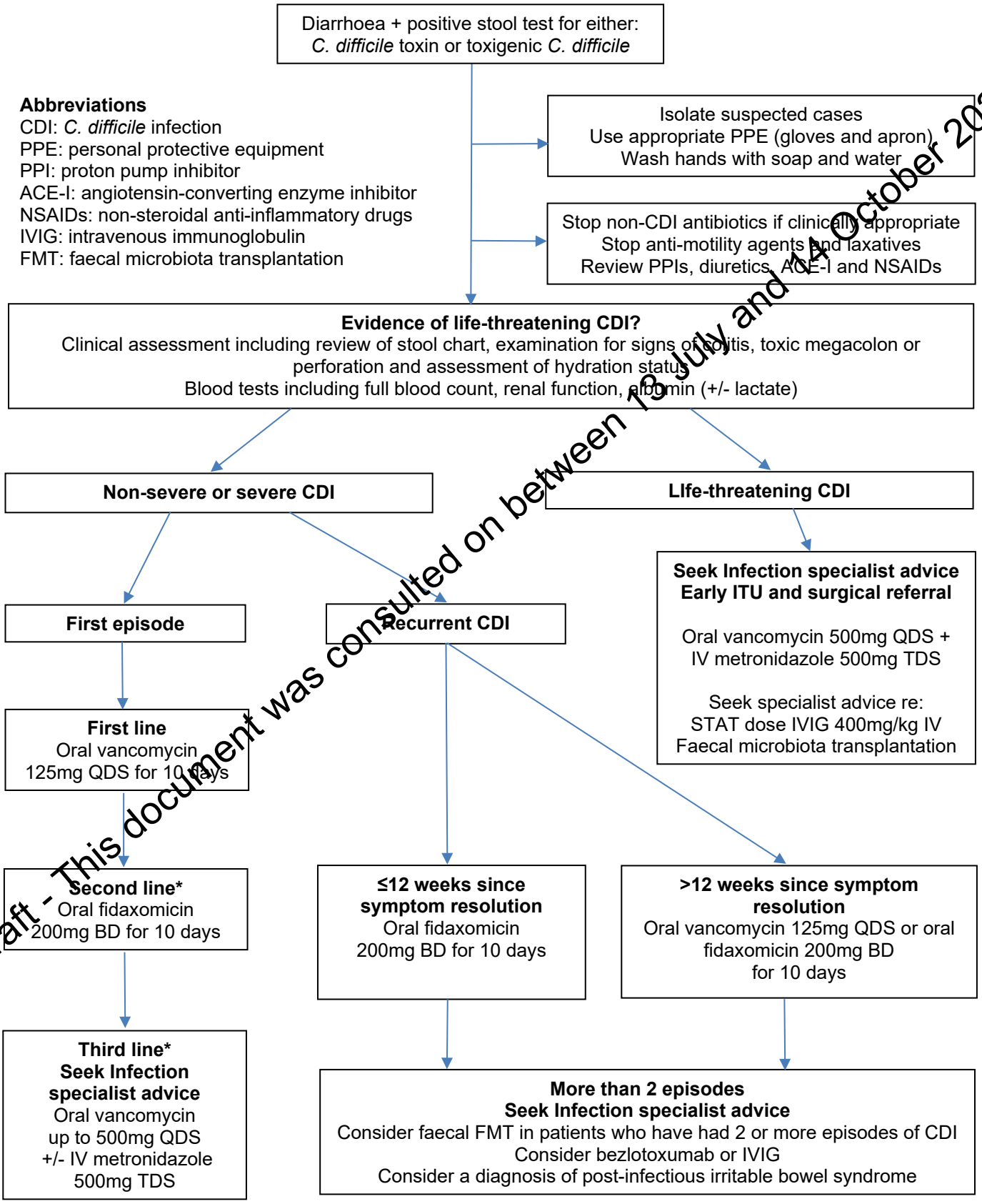
Consider bezlotoxumab or IVIG, especially if there is evidence of malnutrition or wasting.

Post-infectious irritable bowel syndrome (PI-IBS)

Consider a diagnosis of PI-IBS in patients with persistent diarrhoea who are medically stable with normal inflammatory markers. Refer to Rome IV criteria and consider a closely monitored trial of an anti-motility agent such as loperamide (without antibiotics).

Prebiotics and probiotics are not recommended for the treatment or prevention of CDI

4. Treatment algorithm for the assessment and management of CDI



* Note: diarrhoea can take 1 to 2 weeks to resolve

Text alternative for treatment algorithm

Assessment and management of *C. difficile* infection (CDI)

Step 1

Does the patient have diarrhoea plus a positive stool test for either: *C. difficile* toxin or toxigenic *C. difficile*?

If yes, go to step 2.
If no, diagnostic criteria for CDI are not met, explore alternative diagnoses.

Step 2

Ensure appropriate infection control measures are taken, review medication and take these actions:

- isolate suspected cases
- use appropriate personal protective equipment (gloves & apron)
- wash hands with soap and water
- stop non-CDI antibiotics if clinically appropriate
- stop anti-motility agents and laxatives
- review proton-pump inhibitors, diuretics, acetylcholine esterase (ACE) inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs)

Go to Step 3.

Step 3

Assess for evidence of life-threatening CDI by completing a clinical assessment including review of stool chart, examination for signs of colitis, toxic megacolon or perforation and assessment of hydration status and sending blood tests including full blood count, renal function, and albumin (+/- lactate).

Is there evidence of life-threatening CDI?

If yes, go to step 4.
If no, go to step 5.

Step 4

Manage as life-threatening CDI:

- seek infection specialist advice
- early intensive care unit and surgical referrals
- oral vancomycin 500mg four times a day + intravenous metronidazole 500mg 3 times a day
- seek specialist advice for consideration of: STAT dose intravenous immunoglobulin 400mg/kg and faecal microbiota transplantation

End of pathway.

Step 5

Is this a first episode (as opposed to recurrent CDI)?

If yes, go to step 6.
If no, go to step 9.

Step 6

Manage as first episode of non-severe or severe CDI with first line therapy: oral vancomycin 125mg four times a day for 10 days.

Was there a response to treatment? Note: diarrhoea can take one to 2 weeks to resolve.

If yes, go to step 7.
If no, end of pathway.

Step 7

Manage as first episode of non-severe or severe CDI with second line therapy: oral fidaxomicin 200mg twice a day for 10 days.

Was there a response to treatment? Note: diarrhoea can take one to 2 weeks to resolve.

If yes, go to step 8.
If no, end of pathway.

Step 8

Manage as first episode of non-severe or severe CDI with third line therapy: Seek Infection specialist advice, oral vancomycin up to 500mg four times a day +/- intravenous metronidazole 500mg three times a day.

End of pathway.

Step 9

Has it been 12 or more weeks since resolution of symptoms associated with the first episode of CDI?

If yes, go to step 10.
If no, go to step 11.

Step 10

Treat with oral fidaxomicin 200mg twice daily for 10 days.

End of pathway.

Step 11

Have there been fewer than 2 episodes of CDI?

If yes, go to step 12.
If no, go to step 13.

Step 12

Treat with oral vancomycin 125mg for times a day OR oral fidaxomicin 200mg twice a day for 10 days.

End of pathway.

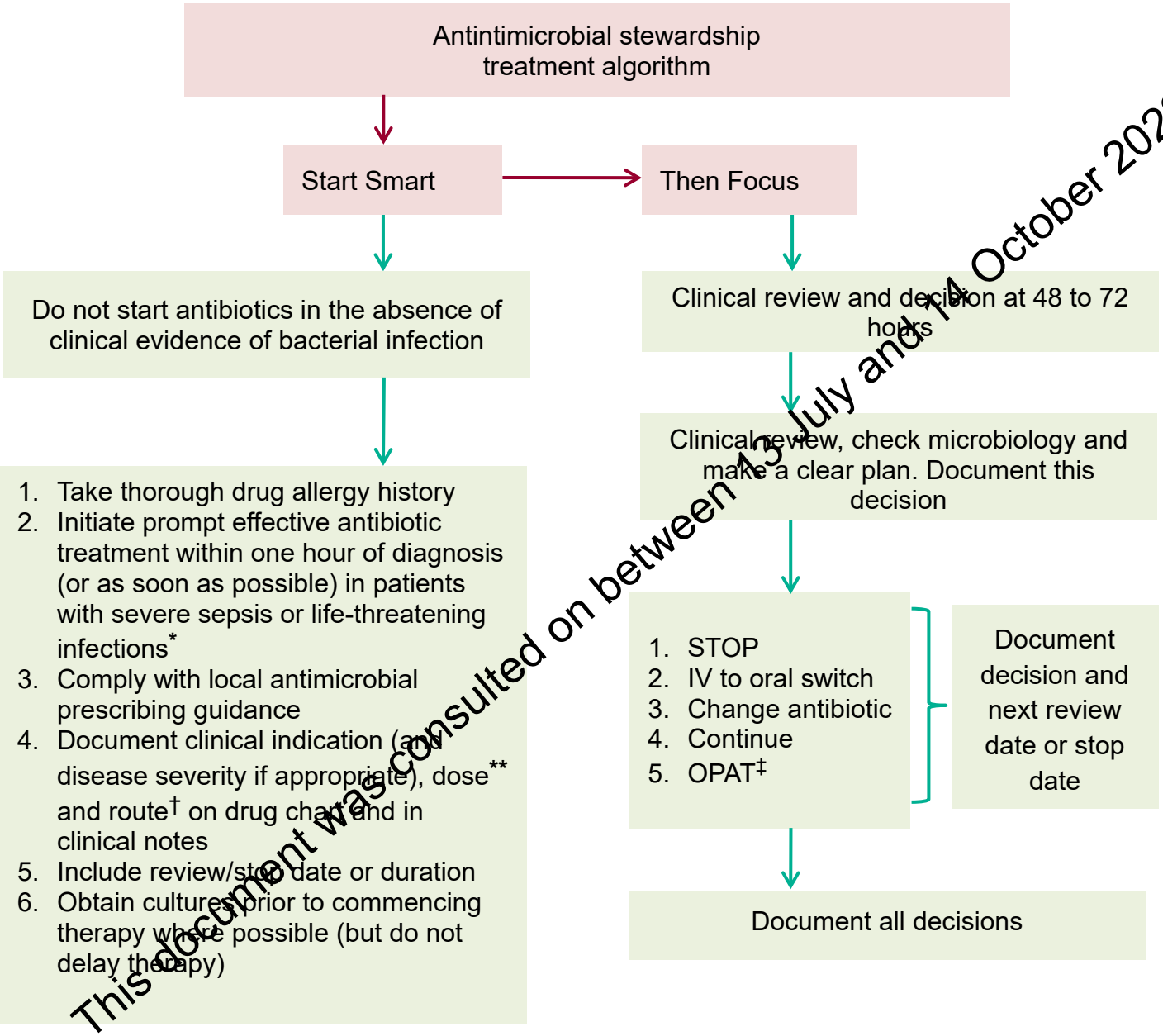
Step 13

For patients with more than 2 episodes of CDI:

- seek infection specialist advice
- consider faecal microbiota transplantation
- consider bezlotoxumab or intravenous immunoglobulin
- consider a diagnosis of post-infectious irritable bowel syndrome

End of pathway.

Appendix 1. Start Smart Then Focus antimicrobial stewardship algorithm



* In accordance with Surviving sepsis patient safety alert
** According to weight or age in children: refer to local formulary or BNFc
† Use appropriate route in line with severity/patient factors
‡ Outpatient parenteral antibiotic therapy

Source: Public Health England (2015). 'Start Smart - Then Focus: antimicrobial stewardship toolkit for English Hospitals'

Accessible text version of the Start Smart algorithm

Pathway 1 Stay Smart

Do not start antibiotics in the absence of clinical evidence of bacterial infection.

1. Take thorough drug allergy history.
2. Initiate prompt effective antibiotic treatment within one hour of diagnosis (or as soon as possible) in patients with severe sepsis or life-threatening infections*.
3. Comply with local antimicrobial prescribing guidance.
4. Document clinical indication (and disease severity if appropriate), dose** and route† on drug chart and in clinical notes.
5. Include review or stop date or duration.
6. Obtain cultures prior to commencing therapy where possible (but do not delay therapy).

Pathway 2 Then Focus

Clinical review and decision at 48 to 72 hours.

Then progress to:

Clinical review, check microbiology and make a clear plan. Document this decision.

Then:

1. STOP
2. IV to oral switch
3. Change antibiotic
4. Continue
5. OPAT (outpatient parenteral antibiotic therapy)

Document decision and next review date or stop date.

Document all decisions.

Notes

* In accordance with the Surviving sepsis patient safety alert.
** According to weight or age in children: refer to local formulary or BNFc.
† Use appropriate route in line with severity or patient factors.

Appendix 2. Interpretation of a 2-step *C. difficile* testing algorithm

Step 3. Interpreting test results

The following actions should be taken depending on the test result:

Result of 2 test algorithm[1]	Interpretation	Include in mandatory reporting to HPA[2]
GDH EIA (or NAAT) positive, toxin EIA positive	CDI is likely to be present	Yes
GDH EIA (or NAAT) positive, toxin EIA negative	C. difficile could be present, so may have transmission potential. Patient could be potential *C. difficile* excretor.	No, but may be suitable for local reporting
GDH EIA (or NAAT) negative, toxin EIA positive	*C. difficile* or CDI is very unlikely to be present, so may have transmission potential. Patient could have other potential pathogens.	No

It must be remembered that no test or combination of tests is infallible and the clinical condition of the patient should always be taken into consideration when making management and treatment choices.

Source: Department of Health (2008). 'Clostridium difficile infection: How to deal with the problem'

[1] A cytotoxin assay may be considered as an alternative to a sensitive toxin EIA, but it yields slower results and this will need to be taken into account in making decisions about infection control.
[2] Unless a repeat sample within 28 days. Please refer to the Mandatory Surveilance Protocol for full case definition and further information.

Appendix 3. The Bristol stool chart

This table shows different stool types, with pictures and verbal descriptions.

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces, a mushy stool
Type 7		Watery, no solid pieces, entirely liquid

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Appendix 4. Acknowledgements

Authors of draft guidance update

Dr Emma McGuire, Clinical Fellow in Infectious Diseases and Microbiology at UKHSA and senior Specialty Training Registrar in Infectious Diseases and Medical Microbiology at Barts Health NHS Trust.

Dr Colin Brown, the Interim Director of Clinical and Emerging Infections within UKHSA, and the Interim Deputy Director responsible for HCAI, Fungal, AMR, AMU, and Sepsis. He is also Director of the WHO Collaborating Centre for Reference and Research on AMR and HCAI and an infectious diseases consultant at the Royal Free Hospital in London.

Dr Jasmin Islam, Consultant in Infectious Diseases and Microbiology at UKHSA and Kings College Hospital NHS Trust.

Specialist advisory sub-group

Professor Mark Wilcox, lead on *C. difficile* infection for UKHSA, National Clinical Director, Antimicrobial Resistance and Infection Prevention and Control for NHS England and Consultant / Head of Microbiology Research and Development and Infection Lead of the Leeds NIHR Diagnostic Technologies Medical Technology and In Vitro Diagnostic Co-operative at Leeds Teaching Hospitals NHS Trust.

Dr Tim Planche, Consultant Medical Microbiologist at St George's University Hospitals NHS Foundation Trust and co-lead for the Infection Care Group and Medical Microbiology clinical lead for South West London Pathology.

Dr Christopher Settle, Consultant Microbiologist South at Tyneside and Sunderland NHS Foundation Trust and chair fo the Healthcare Infection Society.

Dr Bharat Patel, Consultant in Immunology and Microbiology, UKHSA and consultant clinical advisor for the National Institute for Clinical Excellence (NICE) for healthcare associated infections.

Lesley Smith, Infection Prevention and Control nurse at UKHSA.

Dr James Elston, Consultant in Public Health and Infectious Disease Epidemiology at UKHSA.

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UKHSA is an executive agency, sponsored by the Department of Health and Social Care.

Version 1.0

Prepared by: Dr Emma McGuire, Dr Colin Brown and Dr Jasmin Islam along with the subgroup listed in Appendix 4

Published: July 2022
Publishing reference: GOV-12513

UKHSA supports the Sustainable Development Goals