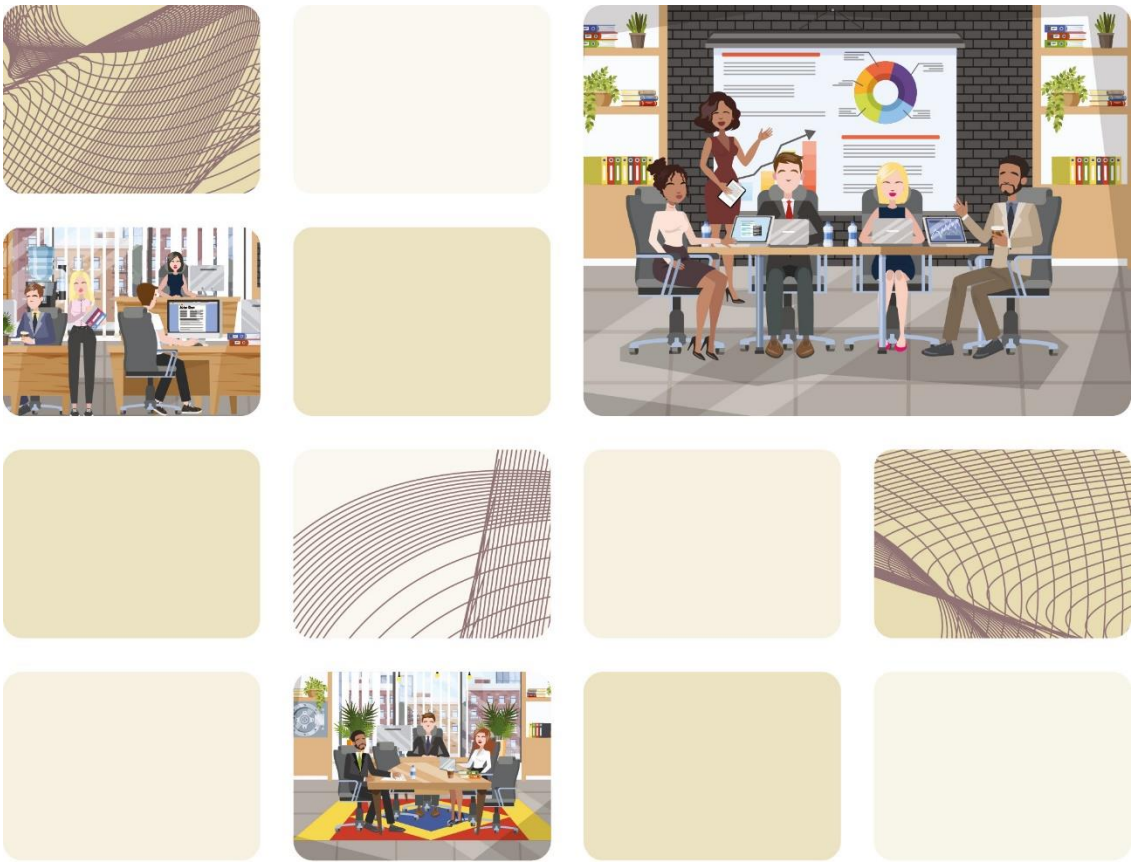
UK Health Security Agency

UK Standards for Microbiology Investigations

Review of users' comments received by Working group for microbiology standards in clinical bacteriology

B 10 Investigation of faecal specimens for *Clostridioides difficile*



This publication was created by UK Health Security Agency (UKHSA) in partnership with the partner organisations.

Recommendations are listed as ACCEPT/ PARTIAL ACCEPT/DEFER/ NONE or PENDING

Issued by the Standards Unit, UK Standards for Microbiology Investigations, UKHSA
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3 Scope of Document

Comment number: 1

Date received: 23/12/2024
Laboratory or organisation name: UK Anaerobe Reference Unit

1. Change ‘discordant’ to ‘inconsistent’.
2. Change ‘test’ to ‘assay’
3. Colonisation/carriage definition – add ‘especially if a patient becomes symptomatic with or without CDI’

Recommended action

1. Accept. This has been changed.
2. Accept. This has been changed.
3. Accept. The statement has been added and moved to section 4.2: Risk factors and course of CDI.

Comment number: 2

Date received: 15/12/2025
Laboratory or organisation name: Royal College of General Practitioners

If it is useful for the lab to see clinical information, such as recent antibiotic use, it may be worth adding that reminder in the document.

Recommended action

1. Accept. This has been added to the scope of the document.

4 Introduction

Comment number: 3

Date received: 23/12/2024
Laboratory or organisation name: UK Anaerobe Reference Unit

Paragraph 1 - As this is a UK SMI should we include data for the other nations too? I’m sure we all have it.

Recommended action

1. None. This paragraph has been removed.

4.1 Pathogenicity

Comment number: 4

Date received: 14/01/2025
Laboratory or organisation name: NHS Countess of Chester

Paragraph 2. Information would be clearer if rewritten as 'In strains which possess the toxin gene, toxin production is controlled by specific genes and can occur in response to various conditions, such as the presence of antibiotics or specific nutrients.' Or something similar

Recommended action

1. Accept. The paragraph has been updated.

4.2 Risk factors and course of *C. difficile* infection

Comment number: 5

Date received: 14/01/2025
Laboratory or organisation name: NHS Countess of Chester

1. Paragraph 3. 'hospital patients' is written twice in the sentence: 'In hospitalised patients, this rate can be as high as 7 - 25% of hospitalised patients (32-35).' But it only needs to be mentioned once.
2. Paragraph 5. It may flow better if the broad-spectrum antibiotic examples in paragraph 5 are mentioned in paragraph 4 at the 1st mention of broad-spectrum antibiotics rather than being repeated twice. E.g., The main risk factor for CDI is the repeated use of broad-spectrum antibiotics, such as 'broad-spectrum beta lactams, cephalosporins, clindamycin and fluoroquinolones (39). that alter or distort the normal microbiota.

Recommended action

1. Accept. The paragraph has been updated.
2. Accept. This sentence has been moved.

Comment number: 6

Date received: 15/01/2025
Laboratory or organisation name: Royal College of General Practitioners

Refers to a peripheral white cell count. I assume this means a blood white cell count which may be clearer.

Recommended action

1. Accept. The text has been updated.

4.3 Treatment and management

Comment number: 7

Date received: 23/12/2024
Laboratory or organisation name: UK Anaerobe Reference Unit

Paragraph 3 - This is English data produced by UKHSA, not UK data. As above, I'm sure the other nations could provide data, if asked.

Recommended action

1. None. This paragraph has been removed.

5.1 Glutamate dehydrogenase antigen detection assays

Comment number: 8

Date received: 23/12/2024
Laboratory or organisation name: UK Anaerobe Reference Unit

1. I think we should make mention here to the fact that 'good' GDH assays are relatively specific. Some labs continue to use an assay that cross-reacts with S. aureus.
2. Change 'confirmatory tests' to 'additional tests'.

Recommended action

1. Accept. A statement highlighting the variation in specificity of GDH assays and kits has been added.
2. Accept. The text has been updated.

5.2 Molecular methods

Comment number: 9

Date received: 14/01/2025
Laboratory or organisation name: NHS Countess of Chester

Paragraph 1 - the word 'and' is not necessary. 'NAATs, and particularly PCR assays, have been used to target *C. difficile* toxin A and B genes in faeces (59).' Could be written as 'NAATs, particularly PCR assays, have been used to target *C. difficile* toxin A and B genes in faeces (59).'

Recommended action

1. Accept. The text has been updated.

5.5.1 *C. difficile* culture

Comment number: 10

Date received: 14/01/2025
Laboratory or organisation name: NHS Countess of Chester

Paragraph 3: comma needed after 'In Scotland'

Recommended action

1. Accept. The text has been updated.

5.6 Typing of *Clostridioides difficile*

Comment number: 11

Date received: 23/12/2025
Laboratory or organisation name: UK Anaerobe Reference Unit

Paragraph 4 - ‘Pure culture or isolate of *C. difficile* is required for typing.’ I’m not sure about the English used here.

Recommended action

1. Accept. Changed to ‘A pure culture or an isolate’.

Comment number: 12

Date received: 14/01/2025

Laboratory or organisation name: NHS Countess of Chester

Paragraph 4 - 'Pure culture or isolate' may sound better as 'A pure culture or isolate'

Recommended action

1. Accept. Please refer to comment above.

8.1 Eligibility criteria for testing:

Comment number: 13

Date received: 30/12/2024
Laboratory or organisation name: Health Services Laboratory, Royal Free Hospital

Health services laboratory (HSL) is a large, centralised, off site lab serving multiple hospitals. For community patients 2-64 years old it is not possible to assess the clinical indications for testing listed, except when *C. difficile* testing is specifically requested. It will not be possible to test all samples for community patients 2-64 years old unless the ICB agrees to pay, which is unlikely as the ICB is actively reducing it's pathology testing costs.

Recommended action

1. None. This was discussed with the working group and the consensus was that UK SMIs represent a good standard of practice, but it was agreed that it is up to the individual laboratories to implement and to make local decisions based on the recommendations.

Comment number: 14

Date received: 31/12/2024
Laboratory or organisation name: UKHSA

The new standards have been changed to indicate CDI testing for all specimens of diarrhoea that are not attributable to an underlying condition, for all patients aged > 2 years old. This change will have substantial additional resource implications for laboratories, and affect the surveillance of CDI as the number of patients tested increases.

To support such a change, in particular for expansion on testing for (ideally all) patients in the community, I expect that there is strong epidemiological evidence that community CDI cases are being under-detected and that this is having clinical or public health harms. However, the paper referenced (Viprey et al) is a European cross-sectional survey and text in the draft which it is based on is being extrapolated from very small numbers.

The IID2 study [1] which was a large community-based GI study, which recruited in 2008 and 2009 (when CDI incidence was higher than now), found that *"C. difficile* is a

very uncommon cause of diarrhoea in the community."

In summary, from an epidemiological perspective, I don't believe that there is a clear evidence at present which would support this change. Should evidence exist which demonstrates a substantial burden of undiagnosed community CDI morbidity, I think this would be a good place to reference it.

Tam CC, Rodrigues LC, Viviani L, et al. Longitudinal study of infectious intestinal disease in the UK (IID2 study): incidence in the community and presenting to general practice Gut 2012;61:69-77.

Recommended action

1. Partial accept. Further supporting references have been added to this section, along with a statement and reference to acknowledge studies that may disagree. It was agreed by the bacteriology working group that the evidence of these papers combined with expert's experience, including input from a patient representative, provides stronger support for the change in testing while also acknowledging the limitations.

Comment number: 15

Date received: 16/01/2025
Laboratory or organisation name: Field Services, Healthcare Associated Infections division, UKHSA

I am not clear nor is the evidence presented as to why the SMI is now recommending testing of community patients under the age of 65 routinely for *C.difficile*.

The list of clinical indications is so vast that it will be a near impossibility for labs to confidently assure themselves they are complying with the SMI for example "abdominal surgery" - would of been helpful to have a time frame on this but reviewing various studies on clinical details provided to microbiology laboratories there is usually very little provided and certainly not enough to cover all these clinical scenarios. Universal testing for *C. difficile* may lead to dual pathogen isolation - e.g. returning traveller with Campylobacter/Shigella/Salmonella (the cause of their diarrhoea) plus an incidental finding of *C.difficile* simply representing colonisation.

I would have thought for the under 65 community patients remaining with only testing for *C.difficile* when specifically requested was a more appropriate recommendation. Although Scotland may have this rule ie testing from over 3s all sample for *C.difficile* is there any evidence this has had any benefit?

The reference given for the justification of universal community testing had a very small number of missed case 8 and the cost of this exercise doesn't seem to have been evaluated nor the consequences of "false positive" *C.difficile* results either on their own or where another pathogen is identified as the pathogen causing *C.difficile.* There would often be a delay in isolating the "true pathogen" e.g. campylobacter will take 48hrs - whereas *C.difficile* result available in less than 24 hrs (in the absence of

universal multiplex PCR) - for all these reasons the proposed move to either universal *C.difficile* testing of community samples (and even using the extensive risk factors as a screen) would appear to need further evaluation prior to putting in the SMI and I would propose to stick to the current wording in the current SMI.

Recommended action

1. Partial accept. This section has been modified to clarify that ‘when clinically requested’ may be used instead of the list of clinical indicators. Some of the indications have been modified to be more specific. A clarifying paragraph has also been added to explain that decisions for testing would be made based on local epidemiology, assessment and liaison with relevant parties. Further references have been added to support the change to testing criteria.

8.2 Specimen type

Comment number: 16

Date received: 23/12/2024
Laboratory or organisation name: UK Anaerobe Reference Unit

Do we need a note here that they are, generally, not a validated specimen type for most NAATs?

Recommended action

1. Accept. Statement added that rectal swabs require validation prior to use.

9.1 *C. difficile* infection diagnostic procedure

Comment number: 17

Date received: 20/12/2024
Laboratory or organisation name: University Hospitals of Leicester NHS Trust

The statement in sections 9 and 10: "A two-stage testing approach with a third test where the primary test is positive and secondary test is negative is required" contradicts the information in table 2 (Interpretation and reporting NAAT followed by Toxin A and B immunoassay) where there is no requirement for a third test if the first test (NAAT) is positive and the second test (Toxin A/B immunoassay) is negative. Suggest: "A two-stage testing approach is required; if the primary test is a GDH immunoassay, a third test is required where this primary test is positive and the secondary test is negative"

Recommended action

1. Partial accept. This statement has been changed to ‘A two-stage testing approach followed by a third test in cases of inconsistent GDH and toxin A/B results’.

10.1 Interpreting and reporting laboratory results

Comment number: 18

Date received: 23/12/2024
Laboratory or organisation name: UK Anaerobe Reference Unit

1. Change ‘single plex’ to *C.difficile* specific NAAT and remove multiplex NAAT.
2. Change ‘discordant’ to ‘inconsistent GDH and toxin A/B’
3. Table 1, line 3 - On reflection this is not correct. The GDH positivity most likely suggests *C. difficile* has been detected, but probably due to a non-toxigenic strain. It’s a bit tricky as we want to avoid the use of the terms toxigenic and infection here.
   Should we be reporting ‘*Clostridioides difficile* Toxin Not detected’ here and then ‘*Clostridioides difficile* Toxin Detected’ where we detect the toxin? In like manner, maybe we should be suggesting *Clostridioides difficile* GDH Detected/Not detected as applicable.

Recommended action

1. None. ‘singleplex’ has been removed. Multiplex NAAT has been replaced by ‘multiplex molecular gastrointestinal pathogen panels’
2. Accept. The text has been updated.
3. Partial accept. ‘Clostridioides difficile toxin’ has been added throughout the table.

10.2 Repeat Testing of Specimens

Comment number: 19

Date received: 23/12/2024
Laboratory or organisation name: UK Anaerobe Reference Unit

1. Paragraph 3 - Can we add in some text (and the appropriate reference) here about toxin clearing in 90% of patients within 7 days as included in the UKHSA document that went for consultation but was never published?
2. Paragraph 5 - I think this will confuse people in light of paragraph 3 I have commented on.

Recommended action

1. None. It was decided that the statement and reference was not required.
2. Accept. This paragraph has been clarified.

11 Mandatory Reporting of *C. difficile* infection

Comment number: 20

Date received: 13/01/2025
Laboratory or organisation name: UKHSA

Thank you for providing this opportunity to feedback on the consultation document. This submission represents the Mandatory Surveillance of Bacteraemia & *C. difficile* Section within AMR & HCAI division within Epidemic & Emerging Infections (EEI) Directorate within Chief Medical Advisor Group of UKHSA. It has been reviewed by my line manager who also works in the Section.

1. Correction as HCAI DCS only covers England.

FROM

England, Wales, and Northern Ireland:

https://hcaidcs.phe.org.uk/ContentManagement/LinksAndAnnouncements/HCAIDCS_Mandatory_Surveillance_Protocol_v4.4.pdf

TO

England:

https://hcaidcs.phe.org.uk/ContentManagement/LinksAndAnnouncements/HCAIDCS_Mandatory_Surveillance_Protocol_v4.4.pdf

2) To add at end of section 11:

For England, there is also a mandatory collection of quarterly aggregated totals of laboratory results (known as QMLR) that includes three variables for:

- Total number of *C. difficile* toxin positive reports in people aged 2-64 years

- Total number of *C. difficile* toxin positive reports results in people aged >65 years

- Total number of stool specimens tested for diagnosis of *C. difficile* infection.

https://hcaidcs.phe.org.uk/ContentManagement/LinksAndAnnouncements/HCAIDCS_Case_Capture_QMLR_UserGuide_V2.0.pdf

Recommended action

1. Accept.

Appendix: Culture

Comment number: 21

Date received: 09/01/2025
Laboratory or organisation name: University Hospitals of Leicester NHS Trust

The heat shock method could be included as an alternative to alcohol shock treatment. Also, regarding stool culture (whether heat or alcohol shock treated) mention that an initial broth enrichment step followed by culturing to plate media enhances the recovery of C.difficile.

Hink T, Burnham CA, Dubberke ER. A systematic evaluation of methods to optimize culture-based recovery of Clostridium difficile from stool specimens. Anaerobe. 2013;19:39-43

Further, include that commercial availability of chromogenic (e.g. CHROMID® Culture Media, bioMerieux) and fluorogenic (CHROMagar *C. difficile*) media are available that remove the need for 'shock' treatment.

Recommended action

1. Accept. The heat shock method, chromogenic media, fluorogenic media and references have all been added.

Appendix: Identification

Comment number: 22

Date received: 09/01/2025
Laboratory or organisation name: University Hospitals of Leicester NHS Trust

Mention that the production of para-cresol is quite unique in C.difficile and the odour is very distinct (like horse manure) - anyone who has worked with C.difficile cultures would recognise that smell especially from a culture plate.

Include the L-Proline aminopeptidase (PRO Disc) test (which is positive) - this is one of the few biochemical tests for which this organism is positive and is a relatively rapid test that can be done from cultures.

Fedorko DP, Williams EC. Use of cycloserine-cefoxitin-fructose agar and L-proline-aminopeptidase (PRO Discs) in the rapid identification of Clostridium difficile. J Clin Microbiol. 1997;35(5):1258-1259

Park KS, Ki CS, Lee NY. Isolation and Identification of Clostridium difficile Using ChromID *C. difficile* Medium Combined With Gram Staining and PRO Disc Testing: A Proposal for a Simple Culture Process. Ann Lab Med. 2015;35(4):404-409

Recommended action

1. None. Odour is not recommended in UK SMIs for health and safety reasons. PRO Disc are no longer widely available in laboratories and therefore is not included.

Financial barriers

Respondents were asked: 'Are there any potential organisational and financial barriers in applying the recommendations or conflict of interest?'.

Comment number: 23

Date received: 23/12/2025
Laboratory or organisation name: UK Anaerobe Reference Unit

Financial barriers may limit the application of NAAT as recommended.

Recommended action

1. None

Comment number: 24

Date received: 13/01/2025
Laboratory or organisation name: Infection Prevention and Control Division. UKHSA

There will be a cost pressure

Recommended action

1. None

Comment number: 25

Date received: 16/01/2025
Laboratory or organisation name: Field Services, Healthcare Associated Infections Division, UKHSA

There clearly will be a cost implication if all samples from the community >2yrs submitted are tested for *C. difficile* and it isn't clear whether this is a useful expenditure as there appears no economic evaluation of the change

Recommended action

1. None

Health benefits

Respondents were asked: 'Are you aware of any health benefits, side effects and risks that might affect the development of this UK SMI?'.

Comment number: 26

Date received: 23/12/2024
Laboratory or organisation name: Infection Sciences department, Severn Pathology

Risk to staff - if alcohol shock method is carried out on an open bench - the use of a Microbiological safety cabinet is recommended.

Recommended action

1. None

Comment number: 27

Date received: 24/12/2024
Laboratory or organisation name: South West London Pathology Network

The clarification of community patients <65 who should be tested for *C.difficile* if they have diarrhoea will result in capturing more community patients with CDI and hopefully prevent/reduce complications

Section 10.2: Repeat testing: it may results in more tests being undertaken however as it will be clinically led, this will reduce complications

Recommended action

1. None

Comment number: 28

Date received: 31/12/2024
Laboratory or organisation name: UKHSA

As stated, the increase in eligibility criteria for testing will affect public health surveillance.

Recommended action

1. None

Comment number: 29

Date received: 13/01/2025
Laboratory or organisation name: Infection Prevention and Control Division, UKHSA

Complexity may delay results

Recommended action

1. None

Comment number: 30

Date received: 16/01/2025
Laboratory or organisation name: Field Services, Healthcare Associated Infections Division, UKHSA

There is a risk of over treatment, the missing of the "true" cause of the diarrhoea or that being later in the processing of the sample e.g. campylobacter positive 48hrs after getting the *C.difficile* result

Recommended action

1. None

Respondents indicating they were happy with the contents of the document

Overall number of comments: 6			
Date received	20/12/2024	**Lab name**	Microbiology, Aminu Kano Teaching Hospital,Kano.
Date received	24/12/2024	**Lab name**	South West London Pathology Network
Date received	03/01/2025	**Lab name**	HCA Laboratories
Date received	13/01/2025	**Lab name**	Infection Prevention and Control division
Date received	04/01/2025	**Lab name**	Keith Shuttleworth and Associates Ltd
Date received	15/01/2025	**Professional body**	Institute of Biomedical Science