WORKING PAPER NUMBER: WP22\_11

**Identifying Clinical Needs for New Diagnostic Tests for Clostridioides Difficile Infection: Results from a Survey of UK Healthcare Professionals**

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**This working paper should cited as:** Cocco P, Davies KA, Smith AF, Messenger MP, West RM and Shinkins B. Identifying Clinical Needs for New Diagnostic Tests for Clostridioides Difficile Infection: Results from a Survey of UK Healthcare Professionals [Internet]. Leeds, University of Leeds, Academic Unit of Health Economics; 2022. Available from <https://medicinehealth.leeds.ac.uk/downloads/download/170/auhe_resources>

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**Additional information**

*Funding*

This work was carried out as a part of the full-time School of Medicine PhD Scholarship awarded to PC by the University of Leeds. This work is also supported by the ‘Antimicrobial Resistance Cross Council Initiative’ (Grant number MR/N029976/1), Funding Partners: The Biotechnology and Biological Sciences Research Council, the Engineering and Physical Sciences Research Council, and the Medical Research Council

*Ethical approval*

This survey was approved by the School of Medicine Research Ethics Committee (SoMREC) at the University of Leeds (application reference number MREC 19-047). The survey was fully anonymised with no direct identifiers of participants (e.g. name, contact details) being recorded.

*Conflict of interest*

PC, KD, AS, RW and BS have nothing to disclose.

MM is an employee of the Medicines and Healthcare Products Regulatory Agency (MHRA). He has previously been a paid consultant/advisor to PinPoint Data Science, UK Department of Health and Social Care, European Union, Cepheid Inc, Boston Healthcare and Simon-Kucher & Partners. KD is currently seconded into UKHSA as Lead Scientific Advisor to the Technologies Validation Group. She has received previous honorarium from Cepheid Inc, and research grants from Alere Ltd, Abbott, Cepheid Inc, and bioMerieux.

The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

*Acknowledgements*

The authors would like to thank Anam Ayaz-Shah, Dr Stephen Bradley, Bryony Dawkins, William Goodman, Kelly Lloyd, Maisie Martland and John O’Dwyer for helping with informally pre-testing the survey. The authors would like to express their gratitude towards Professor Mark Wilcox, Dr Jonathan Sandoe, and Professor Alastair Hay for taking part in the expert-driven pre-testing of the survey. The authors are also grateful to Dr John Coia, Dr Chris Settle, Dr Helen Forrest, Dr David Jenkins and Dr Sarah Mumford for piloting the survey. The authors would also like to thank Dr Beverly Riley and Dr Chris McKee for helping with disseminating the survey.

**Abstract**

**Background**: This survey aimed to assess if there is an unmet clinical need for a new diagnostic test for Clostridioides difficile infection (CDI) in the UK. An online survey was disseminated to UK healthcare professionals with experience in diagnosing CDI.

**Results**: Forty-eight participants completed the survey, most of whom were infection control nurses (n = 21). Due to the lack of an accurate standalone test, a variety of testing algorithms are used across different hospital laboratories. The primary issues identified with current diagnostics for CDI concerned difficulties in identifying who requires testing, and problems with sample collection. Turnaround time was also highlighted as an issue. Key requirements identified for a new CDI diagnostic included (i) quicker turnaround time, (ii) less invasive sample requirements, and (iii) high diagnostic accuracy.

**Conclusions**: These findings should be used to inform the development of new CDI diagnostics in line with the needs of healthcare professionals.

*Key words*: Clostridioides difficile infection; diagnostic; survey; clinical needs; care pathway; development

# Introduction

Clostridioides difficile infection (CDI) is one of the leading causes of healthcare-associated infections, resulting in 124,000 cases and 3,700 deaths across Europe every year [[1](#_ENREF_1), [2](#_ENREF_2)]. Antibiotic treatment is one of the main risk factors for CDI [[3](#_ENREF_3)], with typical symptoms ranging from mild diarrhoea to colitis [[4-6](#_ENREF_4)]. In addition to high morbidity and mortality, CDI is associated with increased healthcare costs and resource use [[7](#_ENREF_7)]. In the UK for example, an observational study published in 2017 estimated an average healthcare cost of £6,294 for patients with a first episode of CDI and an average hospital length of stay of 15 days [[8](#_ENREF_8)].

Diagnostic tests for CDI are part of a multifaceted strategy aiming to control the spread of infection within hospitals [[9](#_ENREF_9)]. In the UK, inpatients with suspected CDI are typically isolated in single rooms while awaiting test results, to prevent in-hospital transmission until confirmation of non-infectious diarrhoea [[10](#_ENREF_10)]. Different testing methods are available for diagnosing CDI, with each test aimed at detecting different analytes of the disease– be it either toxins in stools, the *C.difficile* pathogen or toxigenic strains or, alternatively, a combination of these analytes [[11](#_ENREF_11)]. Tests detecting a single target analyte (i.e. standalone tests) present different advantages and limitations, with none of the current standalone tests being able to accurately and/or quickly identify patients with CDI [[12](#_ENREF_12)]. Combining two or more standalone tests within a testing algorithm is currently regarded as the best strategy for diagnosing CDI [[12](#_ENREF_12), [13](#_ENREF_13)]; in the UK, it is mandatory to run a two-stage testing algorithm for reporting cases of CDI to overcome the shortcomings of each standalone test for CDI [[13](#_ENREF_13)].

Based on the limitations of current diagnostic tests for CDI, there is interest in developing new tests which accurately and rapidly diagnose patients with suspected CDI. While current R&D efforts in this area are in place [[14-16](#_ENREF_14)], the majority of evidence on upcoming tests is currently limited to data on analytical performance, with a paucity of evidence thus far on clinical utility. As research in this area continues to develop, it is crucial that such efforts should be appropriately focused on key areas of unmet clinical need, to ensure that new technologies adopted lead to real improvements in clinical care and patient outcomes. In this study, we conducted a survey of UK healthcare professionals aiming to: (i) assess the areas of current unmet clinical need; (ii) map the clinical care pathway for CDI diagnostics; and (iii) identify key characteristics that new tests for CDI should ideally possess. The findings of this study are intended to help inform the trajectory of future research and development (R&D) activities for novel CDI tests.

# Materials and Methods

## Survey design and development

An anonymised online survey was developed in Online Surveys (formerly Bristol Online Surveys) [[17](#_ENREF_17)] according to best practice methods outlined in the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) [[18](#_ENREF_18)]. The survey comprised of the following sections: (i) description of clinical and laboratory practice; (ii) problems with diagnosing CDI; (iii) room for improvement in current diagnostic tests; and (iv) description of ideal diagnostic test.

The survey was adapted from the Test Evaluation Working Group of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM TE-WG) checklist to identify unmet clinical needs for new biomarkers [[19](#_ENREF_19)]. Checklist questions were customised to the disease area of interest where necessary. The order of certain questions was tailored to respondents’ field of expertise, care setting and knowledge of the disease area, using conditional branching (or ‘*skip logic*’). This feature of online surveys allows alternative questions to be presented based on their response to a current or previous opening question [[20](#_ENREF_20)]. For example, respondents who stated that they did not think that there were any problems with current diagnostic tests for CDI being available in their clinical setting, would not be asked to list the specific limitations with diagnostic tests. A copy of the survey is available in **Appendix A**.

The survey was validated through an iterative pre-testing and piloting process, which included:

1. **Informal pre-testing**: potential respondents were first asked to indicate on a feedback form whether each question was sufficiently understandable, without completing the survey (n=7) [[21](#_ENREF_21)].
2. **Expert-driven pre-testing**: several consultations were then conducted with clinical staff from the Healthcare Associated Infection Research team at the Leeds Teaching Hospitals NHS Trust (n=3), to ensure that survey wording reflected the appropriate terminology for the disease area of interest [[22](#_ENREF_22)]. The clinical experts were asked to *‘think-aloud’* while reviewing the survey without completing any feedback form.
3. **Piloting:** the survey was piloted with the different clinical experts (n=5), to ensure usability and technical functionality of the survey in terms of access, navigations and submission [[23](#_ENREF_23), [24](#_ENREF_24)].

The survey was approved by the School of Medicine Research Ethics Committee at the University of Leeds (MREC 19-047).

## Survey dissemination

The survey was targeted at medical doctors, nurses, healthcare scientists and general practitioners (GPs) with experience of CDI, across hospital and community care settings in the UK. The survey was made available during two rounds of dissemination; the first, between 21st June 2020 and 19th November 2020 and the second, between 29th April 2021 and 1st June 2021. It was disseminated online via (i) social media platforms (Twitter and Facebook); and (ii) three separate mailing lists of UK-based clinical contacts of: the NIHR Leeds In Vitro Diagnostic Co-operative [[25](#_ENREF_25)]; the Rapid infections diagnostics to combat antimicrobial resistance research group (RID-AMR@Leeds) [[26](#_ENREF_26)]; and the Combatting Bacterial Resistance in Europe study (COMBACTE-CDI) [[27](#_ENREF_27)]. The survey was open to anyone who voluntarily clicked the survey link, with no incentives being offered to respondents.

## Survey analysis

Respondents were split into three subgroups: ward-based clinicians (including nurses, consultants and doctors) laboratory-based clinicians, and GPs (for full details see **Table 1**). Descriptive statistics were calculated for close-ended questions, whereas thematic analysis was conducted for open-ended questions. Themes embedded within respondents’ answers were drawn from the key evidence domains underpinning the test evaluation pathway; see **Table 2** for more detail.

Data processing and analysis was conducted in Microsoft Excel, with only completed questions being included in the analysis. All data analysis was conducted by a single analyst [PC], with any uncertainties discussed with the project clinical specialist [KD] and research specialists [BS, AS, RW] as required.

Table 1 Respondents’ subgroups based on job title and care setting where they work

|  |  |  |
| --- | --- | --- |
| Ward-based clinicians | Laboratory-based clinicians | General Practitioners |
| Consultant | Medical Microbiologist | Hospital-based GPs |
| Trainee/Staff Doctor | Biomedical Scientist | Community-based GPs |
| Infectious Disease Doctor | Healthcare Scientist |
| Nurse | Clinical Scientist |
| Infection Control Nurse |

Table 2 Definition of test evidence domains applied during thematic analysis.

|  |  |  |
| --- | --- | --- |
| **Test evidence domain** | **Definition** | **Source** |
| **Target test population** | Factors related to the disease of interest, and selection of which individuals should be tested | [[28](#_ENREF_28), [29](#_ENREF_29)] |
| **Pre-analytical factors** | Factors related to the ‘patient preparation, sample collection, handling, transportation, storage and preparation of testing’ | [[29](#_ENREF_29)] |
| **Analytical performance** | The performance of a test in relation to the analytical phase (i.e. the point of sample analysis). It is the ability of a test to correctly detect and measure a particular analyte (e.g. analytical precision, trueness, analytical sensitivity and specificity, and limits of detection) | [[30](#_ENREF_30), [31](#_ENREF_31)] |
| **Clinical validity** | Ability of a device to yield results that are correlated with a particular clinical condition or a physiological or pathological process or state | [[30](#_ENREF_30)] |
| **Clinical utility** | Ability of a test to affect relevant health-related outcomes for patients (e.g. improvement in quality of life, longer lifespan) | [[32](#_ENREF_32)] |
| **Post-analytical factors** | Factors related to the correct interpretation and reporting of test results | [[33](#_ENREF_33), [34](#_ENREF_34)] |

# Results

A detailed overview of the survey results is provided in **Appendix B**. Key findings are summarised herein. Note that, as certain survey sections entailed conditional branching, the number of participants answering each question may vary.

## Participants

The online survey was disseminated from 21st June 2020 until 1st June 2021 receiving a total of 48 responses. **Table 3** summarises the survey participants. Most of the respondents were infection control nurses (44%, n = 21), followed by consultants (19%, n=9), and healthcare scientists (16%, n=8). The most common clinical setting was the hospital (79%, n=38), with most respondents working in England (88%, n=42). Few respondents reported that they worked in local health authorities (6.3%, n=3) or Public Health – Health Protection (4.2%, n=2).

Table 3 Characteristics of survey participants (e.g. job title, years of working experience, country and clinical setting work setting) in absolute values (n) and as percentages (%).

|  |  |
| --- | --- |
| **Job title** | **n (%)** |
| Infection control Nurse | 21 (44) |
| Consultant | 9 (19) |
| Healthcare Scientist | 8 (16) |
| General Practitioner | 4 (8) |
| Infectious Disease Doctor | 2 (4) |
| Nurse | 2 (4) |
| Medical Microbiologist | 1 (2) |
| Other | 1 (2) |
| **Subgroups** | |
| Ward-based clinician | 33 (69) |
| Laboratory-based clinician | 11 (23) |
| GP | 4 (8) |
| **Years of work experience** | |
| 0 to 4 years | 8 (17) |
| 5 to 10 years | 6 (13) |
| 11 to 15 years | 10 (21) |
| More than 15 years | 24 (50) |
| **Country** | |
| England | 42 (88) |
| Scotland | 3 (6) |
| Northern Ireland | 1 (2) |
| Wales | 2 (4) |
| **Clinical setting** | |
| Hospital | 38 (79) |
| GP medical practice | 5 (10) |
| Other | 5 (10) |

## Description of clinical practice

All ward-based clinicians (n=33) and GPs (n=4) were asked to list the symptoms that would raise suspicion for CDI and which patient age groups were typically suspected of CDI in their clinical setting.

**Figure 1** shows the symptoms that respondents stated would raise suspicion of possible CDI. Out of 37 respondents, watery stools (95%, n=35) and unexplained diarrhoea (95%, n=35) were the most common symptoms leading to suspicion of CDI across each respondent subgroup. Of the remaining symptoms listed, GPs and hospital consultants were more likely to suspect CDI when faced with symptoms of fever and leucocytosis compared to nurses, and consultants were also more likely to consider hypoalbuminemia compared to the other respondents. Among ward-based clinicians and GPs (n=37), older adult patients were reported as the most common patient age group being suspected of CDI (92%, n=34), followed by patients aged between 18 to 65 years old (22%, n=8) – as presented in **Figure 2**. Younger patients were rarely suspected of CDI (8%, n=3).

Except for two respondents, all ward-based clinicians and GPs (n=35) stated that they would request a diagnostic test upon suspicion of CDI and would pre-emptively start infection-control measures while waiting for test results; e.g. single room isolation in the hospital setting, or hand hygiene at the community setting.

Figure 1 Symptoms leading to suspicion of CDI in absolute number (n) and as a proportion of respondents selecting that option within each subgroup (%). The subgroup ‘Nurses’ comprises responses from Nurses (generic) and Infection Control Nurses, whereas the subgroup ‘Others’comprises responses from a General Practitioner and a Public Health officer.

Figure 2 Patient age groups most often suspected for CDI in absolute number (n) and as a proportion of respondents selecting that option within each subgroup (%).

## Description of diagnostic pathway

**Description of testing options**

Among ward-based clinicians who would request testing for CDI (n=33), the majority reported being familiar with the test(s) the laboratory used to diagnose CDI in their clinical setting (88%, n=29). The remaining respondents (12%, n=4) did not answer the next questions on the diagnostic pathway, and moved to the section on **Confidence in test results for CDI.**

Laboratory staff (n=11) and ward-based clinicians familiar with the diagnostic options for CDI (n=29) were asked to describe the laboratory practice for diagnosing CDI in the clinical setting where they worked. Across ward and laboratory-based clinicians (n=40), enzyme immunoassay (EIA) for toxin A/B (75%, n= 30) and glutamate dehydrogenase (GDH) (73%, n=29) were the most common diagnostic tests stated as being available for CDI, followed by Polymerase Chain Reaction (PCR) (48%, n=19). Fewer respondents reported the use of culture (23%, n=9), toxigenic culture (15%, n=6) or cell-cytotoxicity assay (8%, n=3) to diagnose patients with suspected CDI. **Figure 3** summarises the reported availability of CDI diagnostics.

Figure 3 Availability of diagnostic tests for CDI in absolute number (n) and as a proportion of respondents selecting that option within each subgroup (%).

**Testing algorithms for CDI**

Laboratory staff (n=11) and ward-based clinicians familiar with testing options for CDI (n=29) were asked to describe the testing algorithm being used in their clinical setting for diagnosing CDI, if any. Among 40 respondents, the majority of ward and laboratory-based clinicians stated that they would request a testing algorithm for diagnosing CDI (78%, n=31), with a variety of different testing strategies reported; as shown in **Figure 4**. Across 31 respondents, running EIA GDH and EIA toxin A/B (i.e. ‘Option 1’) was the most common testing algorithm reported (52%, n=16), followed by running EIA GDH and PCR (i.e. ‘Option 2’) (16%, n=5), and PCR combined with EIA toxin A/B (i.e. ‘Option 4’) (10%, n=3). The least common option was stool culture followed up by EIA toxin A- B (6%, n=2). For full details of the reported testing algorithms, please see Appendix B.

Figure 4 Testing algorithm options for CDI in absolute number (n) and as a proportion of respondents selecting that option within each subgroup (%). Options with asterisk (\*) might entail a third confirmatory test.

**Confidence in test results for CDI**

All ward-based clinicians (n=33) and GPs (n=4) were asked to state how confident they usually feel about the test results for CDI they receive. Among 37 respondents, the majority reported that they were *‘Fairly confident’* (46%, n=17) or *‘Very confident’* (46%, n=17) about the test results for CDI they receive. Confidence in test results for CDI was mostly based on the perceived high diagnostic accuracy of the testing options being used (n=8). A good correlation between test results and (i) symptoms; (ii) clinical disease of CDI; or (iii) patients’ response to CDI treatment, made the respondents confident in test results for CDI (n=8). Past clinical experience and knowledge of diagnostic assays raised respondents’ confidence in test results for CDI (n=8), as well as support from the laboratory staff working in their clinical setting (n=5). Eight respondents did not answer this question.

## Problems with diagnosing CDI

Each of the total survey participants (n=48) were asked, in an open-ended question, to list any issues currently affecting the diagnosis of CDI; excluding those problems relating to diagnostic tests for CDI (discussed separately in section 3.5). The following sections, together with **Figure 5**, describe the main themes and subthemes that emerged from the data.

**Theme 1: Target test population**

Seventeen respondents commented on the uncertainty surrounding who and when to test for CDI due to a lack of reliable clinical recognition of CDI. Possible explanations provided for this included:

* **Difficulties in distinguishing diarrhoea due to CDI from non-infectious diarrhoea**: diarrhoea is a symptom common to many health conditions and treatments such as antibiotics, thereby making it challenging for clinicians to rule in CDI with confidence, based on episodes of diarrhoea alone.
* **Poor access to patients’ full medical history:** many respondents stressed the challenges in getting a complete clinical background on patients. Clinicians often rely on patients’ self-reporting their current medications, which may lead to incorrect or incomplete information on which antibiotics (if any) patients are receiving. Two respondents noted that patients might be unwilling to share information on antibiotics prescribed by other healthcare workers, such as dentists.
* **Over-reliance on stools frequency and volume:** two respondents commented on the excessive reliance on stool frequency to suspect CDI, rather than considering patients’ underlying conditions and treatments. As clinicians might have an incomplete understanding of patients’ clinical history, suspicion of CDI is often based on the frequency and volumes of stools. Relying on stool frequency, however, was perceived as an inconsistent threshold for suspecting CDI – especially in the context of patients being unwilling to report an episode of diarrhoea in a timely manner.

**Theme 2: Pre-analytical factors**

Most of the respondents referred to pre-analytical testing factors as key issues hindering the diagnosis of CDI (n=19). Eleven respondents highlighted difficulties in obtaining adequate stool samples from patients, especially those suffering from incontinence. Six respondents also mentioned significant delays in sending stool samples to the laboratory for testing.

**Theme 3: Analytical performance**

Five respondents regarded aspects relating to the analytical performance of tests as an issue affecting the diagnosis of CDI, such as delayed time-to-yield test result (n=4), or degradations of toxins over time (n=1). The latter, in turn, can reduce the analytical sensitivity for detecting toxins in stools.

**Theme 4:Post-analytical factors**

Two respondents highlighted challenges in understanding the results of multiple tests being run in a sequence, and as to how the combined results of a testing algorithm link to the disease pathogenesis. Specifically, one respondent noted a poor understanding of the disease pathogenesis (e.g. spores, carriage and active infection) among healthcare workers, whilst a second respondent noted that mixing-up of specimens might cause patients to receive an incorrect stool testing result.

**Theme 5: Clinical utility**

Three respondents referred to delayed time-to-diagnosis as a common issue worsening patient health via delayed time-to-start treatment. One respondent stated that clinicians often rely on stool testing results before starting treatment despite patients having symptoms of CDI. Another respondent commented on the lack of an accurate and rapid point-of-care test (POCT) for CDI, which, in turn, might lead to *‘a lot of side rooms needed at admission and no capacity’.* According to one respondent, delays in receiving test results for CDI might also cause confusion as to whether diarrhoea resolution was due to CDI treatment or to another undetected cause. Another respondent stated the lack of a reliable CDI diagnostic test for patients who remain symptomatic after treatment.

Figure 5 Simplified schematic of the perceived issues with diagnosing patients with CDI

Diagram, schematic

Description automatically generated

**Problems with diagnostic tests for CDI**

Every survey participant (n=48) was asked if there were any issues with current diagnostic tests for CDI being available in their clinical setting, and what problems these limitations might cause.

Over a third of respondents reported problems with current diagnostic tests for CDI (40%, n=19), as opposed to others reporting no issues with CDI diagnostics (25%, n=12) or who were not aware of any limitations (35%, n=17). Specifically, half of the ward-based clinicians did not know if there were any limitations affecting current diagnostic tests for CDI (n=16).

Among the respondents who reported issues with current diagnostic tests for CDI (n=19), the most frequent limitations reported were low diagnostic sensitivity (47%, n=9) and specificity (47%, n= 9), followed by difficulties in interpreting test results (26%, n=5) and long turnaround time (26%, n=5). The most frequently reported consequences of the issues affecting current CDI diagnostics were ‘*Delays in administering treatment to patients’* (47%, n=9), as well as ‘*Inappropriate treatment for CDI’* (42%, n=8) and *‘Differences in case reporting across healthcare facilities’* (42%, n=8). Another common consequence of the limitations of current diagnostics for CDI was ‘*Potential spread of infection’* (37%, n=7).

## Room for improvement

Each of the survey participants (n=48) was asked to state how and if a better diagnostic test would solve any of the abovementioned issues with the diagnosis of CDI.

Over a third of the respondents stated that new diagnostic tests for CDI might help to address the issues affecting the diagnosis of CDI (40%, n=19), whereas others reported an insufficient room for improvement for new CDI diagnostics (19%, n=9), as opposed to several respondents who answered *‘I do not know’* (42%, n=20).

Among those participants who stated that there was insufficient scope for improving new diagnostics for CDI (n=9), two common themes emerged. First, respondents regarded the current testing system combining EIA and PCR, as an efficient and cost-effective method of diagnosing patients with CDI as a result of batch processing and a rapid turnaround time (n=4). Second, respondents claimed that clinical symptoms of CDI would mostly inform decisions as to whether to start antibiotic treatment for CDI and infection-control measures, regardless of laboratory diagnosis (n=2). One respondent mentioned that they were not aware of any limitations with existing CDI tests, whereas the remaining respondents did not answer (n=2).

Of the 19 respondents who noted issues with current CDI diagnostics, the majority agreed that new diagnostic tests for CDI might help to address current problems hindering the diagnosis of CDI (n=16).

## Description of ideal properties for new diagnostic tests

Respondents who stated that there was sufficient room for improvement for new diagnostics for CDI (n=19) were asked to list ideal characteristics for new diagnostic tests such as (i) type of sample; (ii) technique for obtaining the sample; (iii) method for transporting the sample; (iv) turnaround time of testing; (v) positioning of new test into existing care pathway; and (vi) test cost. Among the respondents who claimed that there was enough room for improvement for new diagnostics for CDI (n=19), the following ideal test characteristics were reported:

* **Type of sample**: the most commonly reported ideal type of sample to be tested for CDI was stool (n=15), followed by blood (n=4). One respondent alternatively suggested a rectal swab detecting skin microbes, instead of relying on stool samples being collected. One respondent proposed ‘*a* *sample more accessible than stool*’.
* **Technique for obtaining the sample**: rectal swabs were often recommended as an ideal technique for obtaining the samples (n=7), followed by stool collection (n=5). One respondent suggested that the ideal technique for obtaining samples should be *‘As non-invasive as possible’*, whilst another would avoid stool collection.
* **Technique for transporting the sample**: different suggestions emerged in relation to this test feature. Three respondents suggested transporting swabs in tubes, or alternatively using a chute system or a porter. Three respondents mentioned that testing should be at the point-of-care without the need to transport the sample from the hospital ward to the laboratory.
* **Turnaround time**: eight respondents proposed that the ideal turnaround time for new CDI diagnostics should be less than 1 hour, or within 2 to 6 hours (n=4). One respondent noted that rapid diagnosis of CDI (<2 hours) during emergency admission would be desirable, whereas another stated a preference for a point-of-care rapid test without quantifying the ideal turnaround time.
* **Position in the care pathway**: several respondents recommended that an ideal test should either be point-of-care or ward-based (n=8), or alternatively run as soon as patients are identified as having diarrhoea (n=4).
* **Acceptable cost**: several respondents reported that an acceptable unit cost of a new test would be less than £10 (n=7), followed by a price lower than £30 (n=3) or £50 (n=1). The remaining respondents left this section blank or identified that they did not know how to answer (n=4).

# Discussion

To our knowledge, this is the first survey aiming to scope the unmet clinical need for a new test to diagnose CDI. A Europe-wide study using a Delphi method was conducted in 2014 to establish clinical priorities in the management and diagnosis of CDI patients, however that study did not explicitly define value propositions to drive innovation in new diagnostics for CDI [[35](#_ENREF_35)]. The results of this survey, on the contrary, describe the problems associated with the diagnostic tests for CDI, and the desirable features that a new diagnostic test for CDI should possess. These survey findings are therefore expected to be particularly useful for test manufacturers interested in developing new diagnostic tests for CDI that are ultimately ‘fit for purpose’. In addition to this, findings from this survey describe the current diagnostic pathway for patients suspected with CDI and challenges within that pathway. These findings are therefore of interest to policy makers and relevant bodies in charge of developing national clinical guidelines to understand potential variations in the clinical pathway for CDI across the UK.

**Mapping clinical care pathway for patients suspected with CDI**

Watery stools and unexplained diarrhoea were the main symptoms found to prompt suspicion of CDI across ward-based clinicians – although the frequency and volume of stools was perceived as an inconsistent threshold for suspecting CDI. This survey confirmed that older patients were more frequently suspected of having CDI, and hence tested, whereas younger patients appeared to be underdiagnosed. This finding is consistent with several European epidemiological studies, such as the Longitudinal European Clostridium difficile Infection Diagnosis Surveillance Study (LuCID), EUCLID and COMBACTE-CDI studies [[36-39](#_ENREF_36)].

A range of different CDI tests were used across different hospitals. EIA GDH and EIA for toxin A/B were the most commonly available diagnostic tests. This widespread adoption may be due to the lower cost of EIA, the possibility for batch testing, the quick turnaround time and ease of use [[40](#_ENREF_40), [41](#_ENREF_41)]. Similar findings were found in a survey of 168 English acute NHS hospital trusts laboratories which indicated that EIA for toxin A/B was the most common diagnostic strategy for CDI [[42](#_ENREF_42)]. Following the limitations of each standalone test for CDI, the majority of respondents stated they would run a testing algorithm, as recommended by European [[12](#_ENREF_12)] and UK guidelines for the diagnosis of CDI [[13](#_ENREF_13)]. However, extensive differences were found in the choice of tests being included within a testing algorithm, the order of the tests being run, and whether a confirmatory third test is requested. This finding is unsurprising given the lack of agreement around which reference standard to use for diagnosing CDI and the plethora of markers being correlated with *C.difficile* organism [[43](#_ENREF_43), [44](#_ENREF_44)]. This variability in testing protocols, however, may hinder the comparison of CDI incidence rates across different healthcare facilities using different testing algorithms with varying diagnostic sensitivity and specificity [[42](#_ENREF_42)].

**Issues affecting the diagnosis of CDI**

The survey results indicated that most problems in the diagnosis of CDI revolved around the pre-analytical phase of testing, such as a lack of reliable clinical suspicion for CDI, and difficulties in stool sample collection. As diarrhoea is a side effect common to many conditions and treatments, there was uncertainty around who requires testing. Patients might be tested for CDI unnecessarily, because of a failure in identifying non-infectious causes of diarrhoea, for example; alternatively, their episodes of diarrhoea might go unnoticed due to a lack of clinical suspicion. Poor access to patient clinical history might prevent clinicians from understanding if, and which, antibiotics patients are currently taking. Although the accuracy of patients’ self-reporting of antibiotic usage was found to be relatively reliable [[45](#_ENREF_45), [46](#_ENREF_46)], some survey respondents noted that patients might under-report their antibiotic prescriptions. Significant challenges were also reported with obtaining stools samples, especially in the context of incontinent or unwilling patients. This finding is not unique to CDI diagnosis; it is a widely reported fact that pre-analytical issues are the largest contributor to errors in clinical testing pathways, as opposed to the issues arising in the analytical phase (i.e. sample analysis) where more stringent processes tend to be in place to standardise and automate as far as possible the testing procedures [[47](#_ENREF_47), [48](#_ENREF_48)]. It would appear therefore that for CDI diagnosis, as for most other diagnostic pathways across different clinical areas [[49](#_ENREF_49), [50](#_ENREF_50)], further work is required to improve the pre-analytical phase.

A common perceived limitation of testing options for CDI was poor diagnostic accuracy and long turnaround time-to-test result. There were concerns that these issues lead to delays to treatment or inappropriate treatment. Despite the reported issues, when asked directly whether there were problems with currently available CDI diagnostic tests, most responded by saying that they did not know or that there were no problems.

Survey findings indicate three main areas R&D activities should focus on in relation to new diagnostic tests for CDI, namely enhanced patients’ acceptability to sampling and sample handling, increased diagnostic accuracy and faster turnaround time. There is currently a paucity of data however, as to whether early treatment for CDI, via early diagnosis, can provide a tangible clinical benefit to patients. A prospective time-series study published in 2014, found that receiving a rapid diagnosis for CDI had a positive impact on patient clinical management [[51](#_ENREF_51)]. Further research, however, is needed to confirm the case for improved clinical outcomes resulting from early diagnosis of CDI.

**Desirable features for new CDI diagnostics**

Respondents suggested different desirable properties for new CDI diagnostics. A key requirement concerned the perceived need for new rapid POCTs for diagnosing CDI or, alternatively, with a quick turnaround time (e.g. less than 6 hours).

There was a lack of consensus on the desirable specifications of a new diagnostic test for CDI, especially in relation to pre-analytical and analytical factors. From an analysis perspective, stools were regarded as the ideal type of sample for new CDI diagnostics, however many respondents highlighted the difficulties in collecting stool samples from patients. Some respondents suggested a rectal swab as alternative method of obtaining a sample. Others stated a technique that is as non-invasive as possible. If future tests could be developed to detect markers specific to the *C.difficile* organism based on more widely tolerated sample types (e.g. blood or saliva, as opposed to stool), this would clearly be of benefit. There is clearly a balance required here between what is plausible from a biological perspective and what is preferable to patients and healthcare professionals. Nevertheless, failure to consider patients’ acceptability of sampling method when developing a test could lead to significant delays in sending samples to the laboratory, despite the diagnostic test itself being rapid. There was also a lack of agreement among respondents on whether the test should detect toxigenic strains or active toxin production in stools. This uncertainty reflects an ongoing conundrum hindering understanding of the CDI pathogenesis [[52](#_ENREF_52)].

**Study strengths and limitations**

This online survey had both strengths and limitations. The use of conditional branching questions allowed customisation of the questions being asked depending on the respondents’ field of expertise, clinical setting of interest and knowledge regarding testing options for CDI. This helped to reduce the number of questions asked while also gathering more relevant data. The extensive validation process undertaken ensured the face and content validity of the survey.

This survey however, was based on a convenience sample of UK ward and laboratory-based clinicians and GPs, who saw the survey advertised on social media and volunteered to participate. The generalisability of the survey findings may therefore be limited due to a risk of *‘volunteer bias’*, which is common among open surveys [[18](#_ENREF_18)]. As the research team was not in control of the selection process, only respondents who were interested in filling the survey participated in the study (i.e. *self-selection*) [[53](#_ENREF_53)]. The current survey design therefore failed to prevent multiple entries from an individual respondent, although the likelihood of that occurring is expected to be low. Future versions of this survey could address this issue by excluding responses submitted within an atypical timestamp [[18](#_ENREF_18)]. In addition, questions being asked, or items within multiple-choice questions, were not randomised thereby potentially leading to *question order bias* [[18](#_ENREF_18)]. The software where the online survey was programmed (i.e. Online Surveys) did not allow for randomising items within multiple-choice questions, therefore it was decided against varying the order of questions, as this was heavily dependent on adaptive questioning.

Findings from this survey are generalisable to ward and laboratory-based clinicians working in English hospitals. This study also did not capture the views of other relevant stakeholder groups in the field of CDI, such as hospital managers, patient and industry representatives. Defining unmet clinical needs is a multidisciplinary exercise which requires the input from as many stakeholder groups as possible. Focus groups would help to gauge the views of those stakeholders to whom the survey was not originally sent. This, in turn, could help to reach a broader consensus on the clinical priorities for CDI diagnostics being identified in the survey.

A final limitation of this study is the limited sample size (n=48), and in particular the low number of GPs who responded to the survey (n=4). This may be due to the convenience nature of the sampling; testing for CDI in the community is not as common [[54](#_ENREF_54)] and therefore GPs may not have been as drawn to the survey invitation. The original dissemination of the survey began as the COVID-19 pandemic was gaining force, from April to August 2020. This was an extremely busy period for all healthcare professionals, particularly those working in the field of infection. Attempts to mitigate the initial limited sample size were made by having additional rounds of dissemination, with partial success. To obtain a larger survey response however, future studies of this kind will likely need to wait until the pandemic effect has significantly subsided, or be able to invest substantial efforts into wide-scale recruitment.

While the sample size of this study is considered limited, especially with respect to surveys, it constitutes an improvement in the context of published clinical needs assessment studies based on focus groups, which tend to involve a much lower number of healthcare professionals [[55](#_ENREF_55)]. The survey results were able to capture notable differences in the diagnostic pathways and testing options for CDI across UK hospitals, and highlight common challenges faced by a wide range of healthcare professionals with varying expertise in the diagnosis of CDI. Findings of this survey are therefore expected to be of great interest to test developers, as well as clinicians and policy makers in this setting, to help them understand the current testing practices and perceived challenges with diagnosing CDI.

# Conclusions

This survey highlights key issues UK healthcare professionals face in the diagnosis of patients with suspected CDI. Whilst a key problem identified concerned uncertainty over who to test, we have also identified an unmet need for a new CDI diagnostic, which depends on a less invasive sample type, which is accurate and has a faster turnaround time-to-result. Whilst the survey sample was small, these findings can help to inform and prioritise R&D activities in the CDI diagnostics space, by placing the needs and preferences of the healthcare professionals at the core of the innovation process.

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# Appendix A

**Online survey “Identifying unmet clinical needs in the diagnosis of Clostridioides difficile infection”**

## Information Sheet

You are being invited to participate in a questionnaire which aims to identify any unmet clinical needs in the diagnosis of Clostridioides difficile (*C. difficile*) infection in the UK and to map the current clinical practice. Please read the following information carefully.

**Introduction**. This questionnaire is being conducted as part of a PhD by Paola Cocco at the University of Leeds, under the supervision of Dr Bethany Shinkins, Dr Michael Messenger, Dr Kerrie Davies, Professor Robert West and Dr Alison Smith. This questionnaire was also designed with feedback from Professor Mark Wilcox.

**Why have I been chosen?** We would like to hear your views as you have experience of *C. difficile* infection (medical doctors, nurses, GPs and biomedical scientists) at the hospital and community care setting.

**What will I have to do if I take part?** If you decide to take part, you will be asked your consent to participate at the beginning and again at the end of the questionnaire. This questionnaire will take you approx. 5-10 minutes to complete and does not require you to search for any additional information. Once you submit, it will not be possible to withdraw your responses.

This questionnaire will ask you some questions on care practice for *C. difficile* infection in the clinical setting where you work, your opinion on current diagnostics and if there are any problems with them, what impact these problems have on patient health and how to better address these clinical needs.

**Do I have to take part?** No. Your participation is entirely voluntary and you can withdraw at any point up to submission.

**What are the risks of taking part?** We believe there are no known risks associated with this questionnaire; however, as with any online related activity the risk of a breach is always possible.

**How will my answers be used**? Your participation will remain confidential, and only anonymised data will be published. Further information is available via the University of Leeds [Privacy Notice](https://dataprotection.leeds.ac.uk/wp-content/uploads/sites/48/2019/02/Research-Privacy-Notice.pdf). . Main analyses will be conducted by Paola Cocco with the support of the research team.

**Who has reviewed the study?** Ethical approval has been sought from the School of Medicine Research Ethics Committee at the University of Leeds (reference number MREC 19-047).

**Please continue to complete the survey**.

Many thanks!

**Q1.** Do you consent to participate to this questionnaire?\*[[1]](#footnote-2)

* Yes
* No

*[If answer to Q1, move to Final Page]*

## Respondent Details

**Q2.** What is your main job title?\*

1. General Practitioner
2. Consultant
3. Trainee/Staff Doctor
4. Infection Disease Doctor
5. Medical Microbiologist
6. Nurse
7. Infection Control Nurse
8. Biomedical Scientist
9. Healthcare Scientist
10. Clinical Scientist
11. Other (please specify)

*[If answer to Q2 is a), move to Q3] [If answer to Q2 is b-k), move to Q2a]*

**Q2a.** Please select your specialty\*

* Cardiology
* Chemical Pathology
* Endocrinology
* Gastroenterology
* Geriatric (Elderly Medicine)
* General (Internal Medicine)
* Haematology
* Infectious Diseases
* Infection Prevention and Control
* Intensive Care
* Medical Microbiology and Virology
* Neurology
* Oncology
* Renal Medicine/Nephrology
* Respiratory Medicine
* Rheumatology
* Urology
* Other (please specify)

**Q3.** How many years of experience do you have working in your clinical section?\*

* 0 to 4 years
* 5 to 10 years
* 11 to 15 years
* More than 15 years

**Q4.** Where do you work?\*

* England
* Scotland
* Northern Ireland
* Wales

**Q5.** In which clinical setting do you work?\*

1. Hospital
2. GP Medical Practice
3. Sheltered Accommodation
4. Residential Home
5. Care Services at Home
6. Nursing Home
7. Hospital-based laboratory
8. Independent laboratory
9. Other (please specify)

*[If answer to Q2 is a, move to Q11] [If answer to Q2 is b-d, move to Q6] [If answer to Q2 is f-g, move to Q18]*

*[If answer to Q2 is e, h-j, move to Q7] [If answer to Q2 is k, move to Q6]*

## Field of Expertise

**Q6**. Please select which area of expertise you consider yourself more familiar with.\*

1. Laboratory practice
2. Clinical practice

*[If answer is a), move to Q7] [If answer is b), move to Q18]*

## Laboratory-based clinicians

### Section 1: Description of Laboratory Practice: Testing Option(s)

We would like to gather your views about laboratory practice in diagnosing Clostridioides difficile (*C. difficile*) infection in the laboratory where you work.

**Q7.** Which of the following diagnostic tests are used in your laboratory for individuals with suspected *C. difficile* infection? Please select one or more options.

* Toxigenic culture
* Culture
* Cytotoxicity assay
* Enzyme immunoassay (EIA) for toxin A/B
* Enzyme immunoassay (EIA) FOR Glutamate Dehydrogenase
* Nucleic Acid Amplification Test (NAAT)
* Other (please specify)
* I do not know

**Q8.** Would you run a combination of diagnostic tests (‘testing algorithm’) for a patient with suspected *C. difficile* infection?

1. Yes
2. No
3. I do not know

[if a), move to Q9, if b-c) move to Q27]

### Section 1: Description of Laboratory Practice: Testing Algorithm

**Q9.** For each step of the testing algorithm, please describe in the best way you can what would you do if the test result was positive or negative. If your laboratory uses more testing algorithms please describe them separately.  
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**Q10.** Do you know why this particular testing algorithm is used in your laboratory? If so, please explain.

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[Move to Q30]

## Ward-based clinicians

### Section 1: Description of Current Practice

We would like to gather your views about current practice in diagnosing Clostridioides difficile (*C. difficile*) infection in the clinical setting where you work.

**Q18.** Setting aside treatment regimens, what **symptoms** would lead you to suspect that an individual in your clinical setting has *C. difficile* infection? Please select one or more options.

* Watery stools
* Fever
* Abdominal cramps
* Leucocytosis
* Hypoalbuminemia
* Unexplained diarrhoea
* Other (please specify)
* I do not know

**Q19.** In which age group do you most often encounter individuals with suspected *C. difficile* infection? Please select one or more options.

* Young children (< 2 years old)
* Children (2 to 18 years old)
* Adults (18 to 65 years old)
* Older adults (>65 years old)
* I do not know

**Q20.** As part of this process, would you request any diagnostic test?

1. Yes
2. No

[If a), move to Q20a] [if b), move to Q25]

**Q20a**. Would you presumptively isolate a patient suspected with *C. difficile* infection while awaiting test results?

1. Yes
2. No
3. I do not know

[Move to Q21]

### Description of Current Practice: Diagnostic Pathway (part 1)

**Q21.** Do you know which test(s) the laboratory uses to diagnose individuals suspected with *C. difficile*infection?

1. Yes
2. No

[If a), move to Q22] [if b), move to Q26]

### Description of Current Practice: Diagnostic Pathway (part 2)

**Q22.** Which of the following diagnostic tests would you request to test a patient with suspected *C. difficile* infection? Please select one or more options.

* Toxigenic culture
* Culture
* Cytotoxicity assay
* Enzyme immunoassay (EIA) for toxin A/B
* Enzyme immunoassay (EIA) FOR Glutamate Dehydrogenase
* Nucleic Acid Amplification Test (NAAT)
* Other (please specify)
* I do not know

**Q23.** Would you request a combination of diagnostic tests (‘testing algorithm’) for a patient with suspected *C. difficile* infection?

1. Yes
2. No
3. I do not know

[if a), move to Q24, if b-c) move to Q26]

**Q24.** For each step of the testing algorithm, please describe in the best way you can what would you do if the test result was positive or negative. If your laboratory uses more testing algorithms please describe them separately.  
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[Move to Q26]

**Q25.** For each of the following scenarios, what would you consider to diagnose a patient suspected with *C. difficile* infection (e.g. patient demographics, risk factors, symptoms, underlying conditions and treatment)?

|  |  |
| --- | --- |
| CDI is likely to be present |  |
| *C. difficile* could be present |  |
| CDI is very UNLIKELY to be present |  |

*Cloistridioides difficile infection = CDI*

*Terminology for each diagnostic scenario is based on Department of Health and Social Care document  "Update guidance on the diagnosis and reporting of Clostridium Difficile"(*[*https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\_data/file/215135/dh\_133016.pdf*](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/215135/dh_133016.pdf)*)*

*[Move to Q26]*

### Description of Current Practice: Diagnostic Pathway (part 3b)

**Q26.** Using a scale from 1= "Not at all confident" to 5="Very confident", how confident do you usually feel about the test results for *C. difficile* infection you receive?

* Not at all confident 1
* Not very confident 2
* Neither 3
* Fairly confident 4
* Very confident 5
* I do not know

**Q27.** What is your confidence in test results for *C. difficile* infection based on? Please explain.

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**Q28.** What would make you more confident about test results for *C. difficile* infection?

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

*[Move to Q29]*

### Description of Current Practice: Diagnostic Pathway (part 4)

**Q29.** What would you consider to initiate de-escalation of infection control measures for a patient confirmed with *C. difficile* infection (e.g. test results, patient demographics, risk factors, symptoms, underlying conditions and treatment)?

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

*[Move to Q30]*

## General Practitioners

### Section 1: Description of Clinical Practice (GP)

We would like to gather your views about current practice in diagnosing Clostridioides difficile *(C. difficile)* infection in the clinical setting where you work.

**Q11.** What symptoms would lead you to suspect that an individual in your clinical setting has *C. difficile*infection? Please select one or more options.

* Watery stools
* Fever
* Abdominal cramps
* Leucocytosis
* Hypoalbuminemia
* Unexplained diarrhoea
* Other (please specify)
* I do not know

**Q12.** In which age group do you most often encounter individuals with suspected *C. difficile* infection? Please select one or more options.

* Young children (< 2 years old)
* Children (2 to 18 years old)
* Adults (18 to 65 years old)
* Older adults (>65 years old)
* I do not know

**Q13.** As part of this process, would you request any diagnostic test?

1. Yes
2. No
3. I do not know

*[If a), move to Q13a] [If b-c), move to Q14]*

**Q13a.** Would you suggest a patient suspected with *C. difficile* infection to follow hand hygiene measures after requesting a diagnostic test?

1. Yes
2. No
3. I do not know

*[Move to Q15]*

### Description of Clinical Practice: Diagnostic Pathway (part a)

**Q14.** For each of the following scenarios, what would you consider to diagnose a patient suspected with *C. difficile* infection (e.g. patient demographics, risk factors, symptoms, underlying conditions and treatment)?

*Cloistridioides difficile infection = CDI*

*Terminology for each case is based on Department of Health and Social Care document  "Update guidance on the diagnosis and reporting of Clostridium Difficile"(*[*https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\_data/file/215135/dh\_133016.pdf*](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/215135/dh_133016.pdf)*)*

|  |  |
| --- | --- |
| CDI is likely to be present |  |
| C. difficile could be present |  |
| CDI is very unlikely to be present |  |

*[Move to Q15]*

### Description of Clinical Practice: Diagnostic Pathway (part b)

**Q15.** Using a scale from 1= "Not at all confident" to 5="Very confident", how confident do you usually feel about the test results for *C. difficile* infection you receive?

* Not at all confident 1
* Not very confident 2
* Neither 3
* Fairly confident 4
* Very confident 5
* I do not know

**Q16.** What is your confidence in test results for *C. difficile* infection based on? Please explain.

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Q17.** What would make you more confident about test results for *C. difficile* infection?

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

*[Move to Q30]*

## Common sections

### Section 2: Problems with Diagnosing Clostridioides difficile infection

In this section we are interested in identifying any problems or difficulties with diagnosing *C. difficile* infection in the clinical setting where you work.

**Q30**. In your view, are there any problems in diagnosing C.*difficile* infection? If so, please describe them here.

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Q31**. In your view, are there any problems with current diagnostic tests for C.*difficile* infection?\*

1. Yes
2. No
3. I do not know

*[If answer is a) move to Q32] [If answer is b-c) move to Q34]*

### Section 2. Problems with Current Diagnostic Tests

**Q32.** In relation to the diagnostic test(s) that is available to you in your clinical settings, what are the limitations? Please select one or more options.\*

* Long turnaround time
* Too expensive
* Poor ability to confirm if a patient has *C. difficile* infection
* Poor ability to confirm if a patient does not have *C. difficile* infection
* Difficult to interpret test results
* Other (please specify)
* I do not know

**Q33.** In relation to the diagnostic tests that are available to you in your laboratory, what problems do these limitations cause? Please select one or more options.\*

* Longer length of (hospital) stay
* Inappropriate antibiotic prescription
* Delays in administering treatment to patients
* Differences in case reporting across laboratories
* Potential spread of infection
* Other (please specify)
* I do not know

*[Move to Q34]*

### Section 3: Room for Improvement in Current Diagnostic Tests?

**Q34**. Could a better diagnostic test solve any of the current issues with diagnosing *C. difficile* infection?\*

1. Yes
2. No
3. I do not know

*[If answer is a) move to Q36] [If answer is b) move to Q35a]*

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Q35a**. Please explain your answer.

*[If answer to Q35 is b), move to Q38]*

### Section 4: Description of Ideal Diagnostic Test

**Q36**. How would a better diagnostic test solve current issues with diagnosing C.*difficile* infection?

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

We would now like to collect your thoughts on the ideal features of a new diagnostic test for C.*difficile* infection.

**Q37**. Hypothetically, what would be the ideal characteristics of a new diagnostic test for C.*difficile* infection in relation **to your clinical setting**?

|  |  |
| --- | --- |
|  |  |
| Ideal type of sample (e.g. stool) |  |
| Ideal technique for obtaining the sample (e.g. swab) |  |
| Ideal technique for transporting the sample |  |
| Ideal turnaround time |  |
| Ideal positioning of a new test into care pathway |  |
| Acceptable cost of a new test (£) |  |
| Other ideal features of a new test |  |

### Consent to Submit

**Q38.** Do you consent to submit this questionnaire? Once you submit the questionnaire it will not be possible to withdraw your responses.\*

1. Yes
2. No

*[if answer is a), move to Final page] [if answer is b), move to ‘End of the Questionnaire’]*

### End of the Questionnaire

Many thanks for filling in the questionnaire. Your answers will be deleted as you have chosen not to submit the questionnaire.

Please close this webpage without pressing the button 'Finish'.

If you have any queries, please contact via email Paola Cocco ([umpc@leeds.ac.uk](mailto:umpc@leeds.ac.uk))

*[END QUESTIONNAIRE WITHOUT SUBMITTING IT]*

### Final page

Many thanks for filling in the questionnaire. Your answers will give us great insights on current UK practice for *C. difficile* infected patients.

If you know someone who might be interested in taking part in this questionnaire, please share this link <https://leeds.onlinesurveys.ac.uk/c-difficile-diagnostics>.

If you have any queries, please contact via email Paola Cocco ([umpc@leeds.ac.uk](mailto:umpc@leeds.ac.uk))

# Appendix B

**Table B-1 Summary statistics (n, %) of questions related ‘Description of Clinical Practice’ section, sorted by respondent subgroups**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Would you request a diagnostic test upon suspicion of CDI?** | | | | |
|  | **Total responses (n=37)** | **Consultants and Doctors (n=9)** | **Nurses (n=23)** | **GPs and others (n=5)** |
| **Yes** | 35 (95) | 9 (100) | 22 (96) | 4 (8) |
| **No** | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **I do not know** | 2 (5) | 0 (0) | 1 (4) | 1 (2) |
| **Would you pre-emptively start infection-control measures** | | | | |
| Yes | 36 (97) | 9 (100) | 22 (96) | 5 (100) |
| No | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| I do not know | 1 (3) | 0 (0) | 1 (4) | 0 (0) |
| **Do you know which test(s) the laboratory uses to diagnose CDI?** | | | | |
|  | **Total responses (n=33)** | **Consultants and Doctors (n=9)** | **Nurses (n=23)** | **Others (n=1)** |
| **Yes** | 29 (88) | 9 (100) | 20 (87) | 0 (0) |
| **No** | 4 (12) | 0 (0) | 3 (13) | 1 (100) |
| **I do not know** | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

**Figure B-1 Availability of diagnostic tests for CDI in absolute number (n) and as a proportion of respondents selecting that option within each subgroup (%).**

**Table B-2 Summary statistics (n, %) of a question related to practice of running testing algorithms for CDI, sorted by respondent subgroups**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Would you run a combination of diagnostic tests for CDI** | | |
|  | **Total responses (n=40)** | **Laboratory-based clinicians (n=11)** | **Ward-based clinicians (n=29)** |
| **Yes** | 31 (78) | 10 (91) | 21 (72) |
| **No** | 3 (8) | 1 (9) | 2 (7) |
| **I do not know** | 6 (15) | 0 (0) | 6 (21) |

**Testing algorithm options**

**Option 1 – EIA GDH & EIA toxin A/B**

The most common testing algorithm among ward- and laboratory-based clinicians was testing with EIA GDH, then following up with EIA toxin A/B (n=16). Figure B-1 provides a simplified schematic of testing algorithm ‘Option 1’. Some variations in how to run this testing algorithm were found:

* **order of testing options** – EIA GDH and EIA toxin A/B could be run either simultaneously (n=4), or sequentially with EIA toxin A/B being run following a GDH positive test result (n=12); and
* **need for confirmatory testing** – when the pathogen was detected (GDH positive), many respondents would check for the presence of toxigenic strains of the pathogen using PCR for every sample tested with EIA toxin A/B (n=2), or when free toxins were not found in stools (i.e. EIA toxin A/B negative) (n=12). Only two respondents reported no further testing after the first two steps.

This testing algorithm is often used since it is currently recommended by PHE guidance, as three laboratory-based clinicians explained. ‘Option 1’ testing algorithm appeared to lead to lower testing costs (n=2) – using EIA toxin A/B allows to test more than one sample at once (i.e. *batch testing*) which, in turn, might lead to significant cost savings compared to following-up every sample positive to GDH with PCR. One respondent suggested that this testing algorithm is a clinically- and cost-effective option for diagnosing patients suspected with CDI. Additional advantages of this testing algorithm lied in the reduced time-to-diagnosis and increased ease of use compared to culture.

**Option 2 – EIA GDH & PCR**

Another common testing algorithm among ward- and laboratory-based clinicians was testing first with EIA GDH, then following-up with PCR (n=5). Figure B-1 provides a simplified schematic of testing algorithm ‘Option 2’. Main differences as to how this testing algorithm was run were based on:

* **order of testing options** – EIA GDH and PCR could be run simultaneously (n=1), or in a sequence (n=3); and
* **choice of test for toxins** – since detecting the presence of the pathogen with GDH or toxigenic strains with PCR is insufficient to confirm the presence of CDI, it is recommended to run an additional test for toxins – be it either CCNA (n=2) or EIA toxin A/B (n=2).

Running this testing algorithm helps to quickly de-isolate a non-infectious patient who has tested positive to GDH but negative to PCR, as a laboratory-based clinician explained. Laboratories affiliated with the *C. difficile* ribotyping network (CDRN) are required to run CCNA (n=1), since CCNA is currently one of the gold standards for detecting toxins in stools, as two respondents stated. The combination of EIA GDH, PCR and following-up with EIA toxin A/B appeared to accurately identify carriers and infected cases.

**Figure B-1 Simplified schematic of Option 1, 2 and 3 testing algorithms including of variations within each option**

Diagram

Description automatically generated

**Option 3 – EIA GDH & CCNA**

One respondent suggested testing first with GDH EIA, and if positive to follow-up with CCNA – see Figure B-1.

**Option 4 – PCR & EIA toxin A/B**

A lesser common testing algorithm option was testing first with PCR, then following-up with EIA toxin A/B (n=3). There was some variation as to whether CCNA is used as a confirmative third testing step (n=2) or not (n=1). Since the reported diagnostic sensitivity of EIA toxin A/B is low, it is recommended to run a confirmatory test for toxins to increase confidence in the combined test result. Figure B-2 illustrates a simplified schematic of the ‘Option 4’ testing algorithm.

**Option 5**

One respondent reported testing first with PCR and then EIA GDH (see Figure B-2).

**Figure B-2 Simplified schematic of Option 4 and 5 testing algorithm including variations within each testing algorithm option**

**Diagram

Description automatically generated**

**Option 6**

An additional testing algorithm option was to test first with stool culture and then either follow-up with EIA toxin A/B (n=1) or not (n=1). Figure B-3 gives a simplified schematic of *‘*Option 6’ testing algorithm.

**Figure B-3 Simplified schematic of Option 6 testing algorithm including variation within this testing algorithm option**

Diagram

Description automatically generated

**Table B-3 Summary statistics (n, %) of question related to *‘Problems with diagnostic tests for CDI’* section, sorted by respondent subgroups**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Are there any problems with diagnostic tests for CDI?** | | | | |
|  | **Total responses (n=48)** | **Laboratory-based clinicians (n=11)** | **Ward-based clinicians (n=33)** | **GPs (n=4)** |
| **Yes** | 19 (40) | 6 (55) | 11 (33) | 2 (50) |
| **No** | 12 (25) | 5 (45) | 6 (19) | 1 (25) |
| **I do not know** | 17 (35) | 0 (0) | 16 (48) | 1 (25) |
| **Is there room for improvement for new diagnostic tests for CDI?** | | | | |
| **Yes** | 19 (40) | 7 (64) | 10 (30) | 2 (50) |
| **No** | 9 (19) | 4 (36) | 4 (12) | 1 (25) |
| **I do not know** | 20 (42) | 0 (0) | 19 (58) | 1 (25) |

**Table B-4 Desirable specifications new diagnostic tests for CDI should ideally possess according to respondents (n=19), sorted by themes and subthemes in absolute number (n) and as a proportion of respondents which discussed that theme (%).**

|  |  |
| --- | --- |
| **Ideal type of sample** | **n (%)** |
| Stool | 15 (79) |
| Blood | 4 (21) |
| Saliva | 1 (5) |
| Skin microbes | 1 (5) |
| Other | 1 (5) |
| N/A | 1 (5) |
| **Ideal technique for obtaining the sample** |  |
| Rectal swab | 7 (37) |
| Stool collection | 5 (26) |
| Others | 5 (26) |
| N/A | 2 (11) |
| **Ideal technique for transporting the sample** |  |
| Tube | 3 (16) |
| Chute | 1 (5) |
| Porter | 1 (5) |
| Ward-based/ no need for transportation | 2 (11) |
| Ambient/unrefrigerated | 2 (11) |
| Other | 6 (32) |
| N/A | 2 (11) |
| **Ideal turnaround time** |  |
| < 1 hour | 8 (42) |
| < 2 hours | 2 (9) |
| 2 – 4 hours | 2 (11) |
| 6 hours | 2 (11) |
| 24 hours | 3 (16) |
| N/A | 1 (5) |
| **Ideal positioning of a new test into care pathway** |  |
| Point-of-care | 8 (42) |
| Symptom onset | 4 (21) |
| N/A | 6 (32) |
| **Acceptable cost of a test** |  |
| ≤ £10 | 7 (37) |
| < £30 | 3 (16) |
| <50£ | 1 (5) |
| £80 | 1 (5) |
| Free | 2 (11) |
| N/A | 4 (21) |
| The absolute number of respondents might not add up to 19 in case respondents proposed more than one subtheme for each desirable specification | |

1. \* indicates a mandatory question [↑](#footnote-ref-2)