



***Clostridium difficile:***  
**Findings and recommendations**  
**from a review of the epidemiology**  
**and a survey of Directors of**  
**Infection Prevention and Control in**  
**England**

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# ***Clostridium difficile*: Findings and recommendations from a review of the epidemiology and a survey of Directors of Infection Prevention and Control in England**

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## Executive summary

This report summarises the main issues facing professionals dealing with the detection, prevention and control of *Clostridium difficile* infection (CDI) in England. It comprises the findings from a review of the epidemiology of *C. difficile* and the final results from a survey of Directors of Infection Prevention and Control (DIPCs) on CDI prevention and control. The latter supplements findings included in a preliminary report that was published jointly with the Healthcare Commission in December 2005<sup>1</sup>. It does not deal with the treatment of infection.

In common with several other developed countries, the number of reported cases of CDI in England and Wales has increased dramatically during the past decade. This probably represents increases in ascertainment and reporting alongside real increases in numbers of new cases. There are also concerns that CDI is more likely than previously to affect younger age groups, though the evidence for this is as yet inconclusive. Alongside these developments, the proportion of CDI in England caused by the ribotype 027 strain has increased substantially in the last few years. This strain has been characterised as a hypertoxin-producer, and has been associated with CDI outbreaks in which greater than average severity of CDI and mortality, together with high attack rates in the elderly and unusual numbers of cases in younger people, were reported. This report recommends that the objectives and adequacy of existing information systems (including surveillance) for detecting and interpreting changes in the epidemiology of CDI should be reviewed.

Current national surveillance of CDI provides information on incidence and causative strains, but not on severity. Surveillance of incidence includes voluntary reporting of laboratory reports of *C. difficile* in people of all ages, and mandatory reporting of cases in people of 65 years or older. The survey found that testing and reporting of cases for the purposes of mandatory surveillance were inconsistent. There is substantial uncertainty about the scheme's benefits, and concerns that it unfairly penalises trusts whose laboratories process significant numbers of samples from non-acute trust sources, particularly community cases. Consideration should be given to improving four aspects of CDI incidence surveillance: accuracy (principally, adherence to criteria for testing and reporting samples for the mandatory case reporting scheme); descriptiveness (primarily, submission of data on the healthcare source of reported cases and samples); completeness (for instance, improving

surveillance in people of 65 years or younger), and comparability (ensuring that methods of obtaining trust and regional incidence are fair, including addressing the possible impact of community cases on these rates).

Monitoring of *C. difficile* strains takes place through the random sampling scheme. Although participation is extensive, there is confusion about the scheme's status. The continuing objectives of this programme should be reviewed so that recommendations on its future implementation can be made. Hospital surveillance is widespread, and is usually concerned with local incidence and risk factors for CDI. The value of introducing systematic monitoring of basic markers of clinical severity, or major risk factors for CDI (particularly antimicrobial prescribing), should be reviewed.

Both detection and reporting of outbreaks are incomplete and inconsistent. Processes for ensuring that CDI outbreaks are reported to the Health Protection Agency and other healthcare organisations in a timely and consistent manner should be reviewed.

Over 90% of laboratories use a recommended diagnostic test for CDI, based on detection of toxins A and B – a major improvement compared to 2002. However, criteria for requesting *C. difficile* culture for further microbiological investigations such as strain typing vary substantially, presumably because the value of these tests remains unclear to many microbiologists and infection control clinicians. The report recommends that guidance on the use of culture and typing should be reviewed.

Most trusts now have specific policies for dealing with cases of CDI, though some still do not. Nevertheless, the very wide variation in infection rates in acute trusts in England indicates that there is room for improving adherence to internal policies, as well as external recommendations for prevention and control of CDI. A majority of trusts do not isolate all cases of CDI, and almost half do not do so routinely; many DIPCs identified a lack of isolation facilities as a key barrier to effective management of *C. difficile* outbreaks. Adherence to good antimicrobial practice is also hard to appraise, given the dearth of comparative hospital prescribing information. The increased incidence of CDI, possible changes in this infection's average severity and population distribution, and the emergence of new and possibly hyper-virulent strains of *C. difficile* highlight the need to review currently recommended procedures for prevention and control of CDI, particularly as regards adherence to recommendations on isolating cases and implementation of robust antimicrobial policies.

### Summary of Recommendations

1. Existing information sources should be reviewed to ensure that these adequately detect and interpret trends in the incidence, distribution and severity of *C. difficile* infection. The value of obtaining data to monitor trends in CDI clinical severity of CDI should be balanced against the practical difficulties of collecting such data.
2. National surveillance of *C. difficile* should be improved to ensure a consistent approach nationally to the consideration and diagnosis of infection, reporting of cases, reporting of healthcare source, definition of outbreaks and hyperendemic situations and the reporting of outbreaks. This should also consider mechanisms for collecting hospital prescribing data nationally for comparative purposes.
3. Methods of amalgamating the strengths of the voluntary and mandatory CDI incidence surveillance systems should be explored, to avoid duplication of effort.
4. The continuing objectives of the random sampling programme should be reviewed to make recommendations on its future development.
5. Strengthening international networks for monitoring and communicating information on *C. difficile* strains should be considered.
6. Laboratory methods for detecting *C. difficile* should be reviewed to ascertain the accuracy and reliability of recommended diagnostic tests for *C. difficile*.
7. Guidelines on the use of *C. difficile* culture for further microbiological investigations, including strain identification, should be reviewed and disseminated.
8. Existing recommendations for the prevention and control of CDI should be reviewed, to ensure that these: adequately promote adherence to recommendations on good antimicrobial practice, isolation of patients, and environmental cleaning and hygiene; specify procedures for reporting and managing outbreaks of CDI, including in areas with hyperendemic disease; and reflect research conducted since the 1994 guidance on *C. difficile* prevention and control.
9. There is an urgent need for research into possible recent changes in the epidemiology of CDI, including the contribution of ascertainment to rising CDI rates, the transmissibility and clinical severity of particular *C. difficile* strains, and the impact of community cases on disease burden.

## 1. Introduction

### 1.1 Background

*Clostridium difficile* is increasingly in the news<sup>2:3</sup>. Although meticillin-resistant *Staphylococcus aureus* (MRSA) has dominated the debate on healthcare-associated infections in the UK in recent years, there is now a growing awareness that infections with *C. difficile* also pose a significant risk to the public health. There are three main reasons for this: reports suggesting that incidence of this disease has increased rapidly in recent years; the emergence, or new awareness of, highly-virulent bacterial strains causing outbreaks of *C. difficile* infection with high mortality in several countries (including the UK); and anecdotal evidence that infections in people previously thought to be at lower risk are increasing<sup>4-7</sup>.

This report summarises the main issues that currently face professionals dealing with *C. difficile* prevention and control in England, arising from a review of the epidemiology, and the findings from a questionnaire survey of Directors of Infection Prevention and Control (DIPCs) in England on aspects of *C. difficile* detection, surveillance, prevention and control. To emphasise their public health context, these findings will be presented alongside a discussion of the major issue/s to which they relate. It is hoped that this will highlight the rationale for any recommendations for changing current practice based on survey findings.

The findings from the survey of DIPCs in England supplement those included in a preliminary report that was published jointly with the Healthcare Commission in December 2005<sup>1</sup>. The respective roles of the Health Protection Agency (HPA) and Healthcare Commission are described in Appendix 1.

### 1.2 *Clostridium difficile*

*C. difficile* infection (CDI) is the most commonly diagnosed bacterial cause of infectious hospital-acquired diarrhoea in developed countries. *C. difficile* is an anaerobic spore-forming gram positive bacterium that causes a spectrum of clinical syndromes: some people have the bacteria and / or their spores in faeces without symptoms; however, most develop diarrhoea which, in severe cases, leads to pseudomembranous colitis and sometimes death. Disease is caused by the effects of bacterial cytotoxins which cause haemostasis and tissue necrosis, predominantly in the colon<sup>8</sup>. Recent treatment with antibiotics is, in most cases, a prerequisite for the development of CDI<sup>9</sup>. Although broad spectrum antibiotics are most often associated

with the disease, any antimicrobial agent can precipitate it. Certain groups of people are particularly at risk of developing CDI; these include the elderly, those who have recently had surgery, and people with serious underlying diseases. Recurrence of CDI is common, but it can be difficult to differentiate relapse from a new infection in the same person.

*C. difficile* produces spores that can later develop into vegetative bacteria. Spores are resistant to heat, alcohol and stomach acid, and can therefore survive in the environment for long periods. These factors facilitate the transmission of *C. difficile*: spores from infected patients may contaminate the environment, allowing transmission of infection to vulnerable patients.

Management of *C. difficile* involves treatment of infected patients, as well as infection control measures to prevent and control further spread of infection. The former requires discontinuation of any precipitating antibiotics, where possible, and treatment with specific antibiotics effective against *C. difficile*. Recommended measures to prevent and control *C. difficile* include prudent use of antibiotics, attention to hand hygiene and environmental cleanliness, early detection of cases and isolation of affected patients to prevent direct spread as well as contamination of the neighbouring environment.

### 1.3 The *C. difficile* survey

In October 2005, the Centre for Infections (CfI) at the HPA and the Healthcare Commission jointly undertook a survey on the detection, prevention and management of *C. difficile* in England. The involvement of the Healthcare Commission stemmed from its investigation into outbreaks of CDI at Stoke Mandeville Hospital, part of Buckinghamshire Hospitals NHS Trust. The Healthcare Commission was charged with undertaking this investigation by the Secretary of State for Health in June 2005. To gain an understanding of the issues facing NHS hospitals in relation to *C. difficile* as part of this investigation, the Healthcare Commission collaborated with the HPA in conducting this national survey (henceforth referred to as “*the survey*”).

The survey had input from key individuals in the field, including senior microbiologists, members of the former national *C. difficile* Standards Group, and the Department of Health. Comments were also incorporated from the DIPCs of 16 trusts

who took part in a pilot of the survey. The survey was sent to DIPCs at all 173 acute hospital trusts in England.

Interim results from 118 trusts (68%) were published on the HPA and Healthcare Commission websites in December 2005<sup>1</sup>. Completed questionnaires were eventually received from 150 trusts, giving a return rate of 87%. Findings from these are presented here. For the purposes of analysis trusts were classified in two ways: first, whether they were specialist teaching, single specialty or district general hospital trusts; second, according to the incidence of CDI as measured by the first year of results from mandatory surveillance.

## 2. Epidemiology of *C. difficile* infection: review of the data

There are widespread concerns that the incidence of CDI has increased rapidly during the past decade, that these infections are occurring more frequently in groups previously considered at lower risk for the disease, and are becoming more severe. In this section the evidence for these concerns, including relevant findings from the *C. difficile* survey, are discussed.

### 2.1 Incidence

#### 2.1.1 England

In England, incidence has been studied using laboratory and case reports, death certifications and hospital diagnoses.

Surveillance of positive *C. difficile* laboratory reports was introduced in 1990 on a voluntary basis as part of the Public Health Laboratory Service (PHLS) surveillance programme for infectious diseases caused by the main human pathogens (part of the PHLS was incorporated into the HPA). Most of this information is received through electronic reporting to the HPA's database (LabBase) by laboratories; the remainder is obtained from paper records. Additional information on reported cases may include patient details such as age and sex, details of detection methods used, and some antibiotic susceptibility results. Between 1990 and 2004, the number of laboratory diagnoses of *C. difficile* reported through this system increased from 1172 reports per year (1990) to 46,501 (2004)<sup>10</sup>.

Since January 2004, acute trusts in England have been required to report all cases of CDI in people of 65 years and over as part of the Department of Health's (DH) programme of mandatory surveillance of healthcare associated infections<sup>11-13;13</sup>. Results from the first two years of this reporting scheme appeared to confirm ongoing increases in numbers of infections: there were 44,107 cases of CDI in people of 65 years or older in 2004, and 51,690 cases in 2005<sup>14</sup>. This represented an increase in CDI from 555 to 638 cases per 100,000 people of 65 years or older from 2004 to 2005.

Trends in disease and mortality associated with CDI infection are currently the subject of a joint project between the Office for National Statistics (ONS) and the HPA<sup>15</sup>. ICD-10 coded death registrations data (1999; 2001-2004) held by ONS are

being used to determine the overall age, sex and region-specific incidence of mortality from CDI in England and Wales. Trends in incidence of CDI are being examined using Hospital Episode Statistics (HES) from 1998/99 to 2003/04. Preliminary analyses of deaths occurring between 2001 and 2003 where *C. difficile* associated disease was specified as the underlying cause have shown an increasing trend: 531 deaths in 1999, 756 in 2002, and 1245 in 2004. Approximately two-thirds of these deaths were in women. These early results suggest that the reported increase in laboratory confirmed cases of *C. difficile* is being reflected in a growing burden of mortality. Analyses using HES data have yet to be undertaken.

#### 2.1.2 Other countries

There is good evidence that similar increases in the reported incidence of CDI have occurred in other developed countries during the past decade. In Quebec, Canada, incidence rose approximately four-fold between 1997 and 2004<sup>16</sup>. Even greater increases were reported from smaller areas within Quebec: one hospital reported that incidence had increased eight-fold from 1991-2003 among people of 65 years or older<sup>17</sup>. The period from 2002 coincided with a large and widely distributed outbreak of *C. difficile* in parts of Quebec, and it is noteworthy that data from some Quebecois hospitals show that cases in 18-64 year olds did not increase until 2003.

In the USA, data from a variety of sources have suggested that the incidence of *C. difficile* is increasing<sup>18;19</sup>. First, annual *C. difficile*-associated disease (CDAD) diagnoses in selected US hospitals with over 500 beds showed a steady increase from 1980-2001. A national survey of over 300,000 discharges from US acute care hospitals estimated the national rate of CDAD by projecting the number of times CDAD was listed as a diagnosis on a discharge form to all discharges from US acute care hospitals. This indicated that rates of CDAD increased rapidly after 2000. These increases were most pronounced in older age groups but were also seen in younger age groups.

#### 2.1.3 Possible explanations for increasing rates

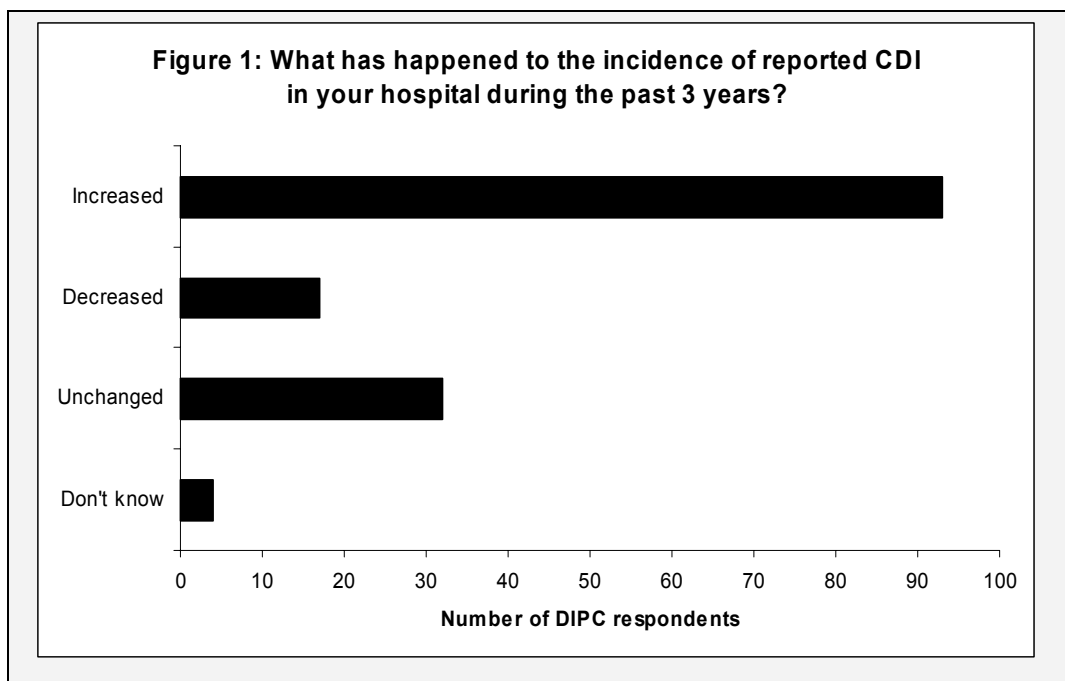
*Increased ascertainment:* The rising incidence of CDI has occurred at a time during which professional awareness and laboratory facilities for diagnosing the disease have improved. Therefore, changes in incidence may merely represent increased ascertainment of cases rather than an actual increase in the numbers of people with CDI. Reporting of *C. difficile* is very likely to have increased in the past ten years; this is evidenced by the rising proportion of laboratories in England that report

electronically to the HPA, and the increasing incidence of many organisms reported during this period. It is difficult to quantify the contribution that greater ascertainment has made to the increased reported incidence of CDI.

*Increased numbers of cases:* There are strong reasons for suspecting that a concurrent real increase in the numbers of people developing CDI infection has occurred. First, quantitatively and temporally similar increases in rates of CDI have been reported in several countries; it is unlikely that levels of ascertainment have increased similarly in all of these countries at the same time. Second, increases in incidence have been reported using a range of measures, including laboratory reports, hospital discharge diagnoses, and rates of complications such as colectomies, which are unlikely to have been similarly affected by increased awareness and diagnostic vigour. Third, surveys of professionals provide anecdotal evidence of real changes in clinical incidence. For example, nearly 40% of US infectious disease physicians questioned in 2005 had perceived an increase in cases of *C. difficile* during the preceding two years<sup>6</sup>. The CDI survey found that a similar proportion (49%) of DIPCs in England thought that rates of CDI had increased at their trust in the previous three years (Box 1).

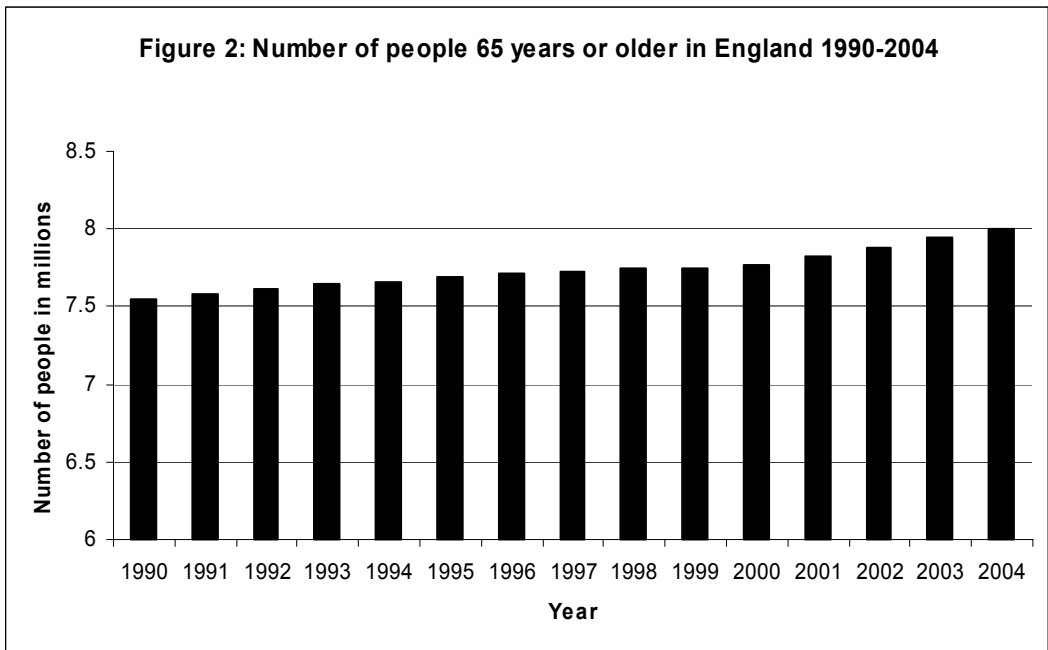
Box 1: Views of DIPCs on incidence of CDI at their trusts

64% (93/150) of responding DIPCs in England said that the reported incidence of *C. difficile* infection at their trusts had increased during the previous three years. A further 11% (17/150) thought it had decreased and 21% (32/150) thought it had not changed (Figure 1). With respect to factors contributing to a reported increased incidence, 86% (74/86) of those who replied cited increased numbers of cases while 79% (71/89) cited increased ascertainment. Although the factor cited most frequently as the “most important cause” of any reported increase was “increased ascertainment” (40%), 56% of responses mentioned “increased numbers of sporadic cases”, “increased hyperendemicity (continuous high level incidence rather than repeated outbreaks)” or both. Overall, 49% (74/150) of DIPCs had perceived an increase in numbers of *C. difficile* cases during the past three years. This figure is similar to that reported from the USA<sup>6</sup>.

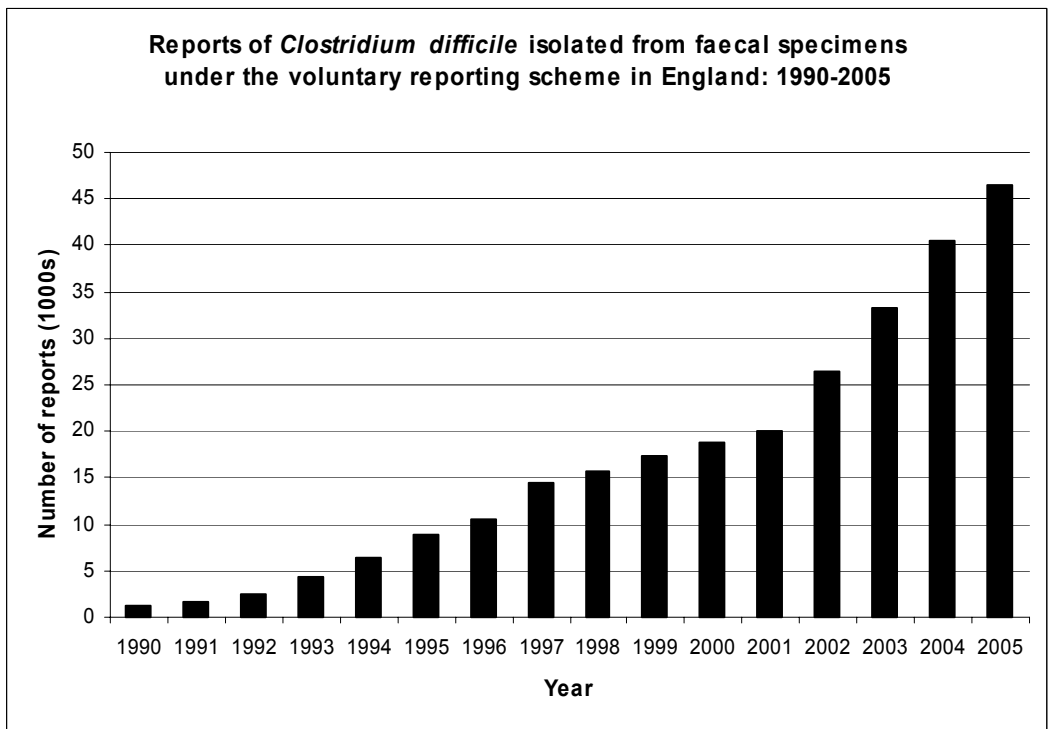


If increases in the reported incidence of CDI are due at least partly to increased numbers of cases, the obvious question is why have these occurred? There are several possible explanations, which are briefly considered below.

*Increasing numbers of people at risk:* Many or most cases of *C. difficile* during the past decade have occurred in people with well-known risk factors for *C. difficile*, particularly the elderly and those with concurrent medical or surgical disease. Thus it has been suggested that any real increase in *C. difficile* incidence during the past decade is due to increases in the number of people at particular risk of *C. difficile*; indeed, the 1994 Working Party Report on *C. difficile* predicted increases in *C. difficile* due to rising numbers of elderly people in the UK<sup>20</sup>. However, comparison of the respective rates of increase in the numbers of elderly people and the numbers of reported cases of CDI in England (Figures 2 and 3) shows the former has increased only moderately, while the latter has increased dramatically. Clearly, other factors are also involved.



**Figure 3: *C. difficile* laboratory reports in England 1990-2005**



### *Other explanations for increasing numbers of cases of CDI*

These can be divided into explanations citing an increase in factors known to cause infections with *C. difficile*, and those blaming new factors thought to cause increased spread of CDI. Thus suggestions for a real increase in the frequency with which people develop CDI include the emergence of strains with increased virulence, antimicrobial resistance or both; changes in antibiotic prescribing; increased use of proton pump inhibitors; overcrowding in hospitals; increasing transit in healthcare institutions (for instance, the increasing propensity for patients admitted to hospital to be moved from one ward to another); lower standards of hygiene and environmental cleaning following reductions in housecleaning staff and outsourcing of hospital cleaning contracts; and increased incidence of *C. difficile* in farm animals<sup>4-6;21;22</sup>. The evidence for most or all of these propositions is weak or contradictory. For example, there are few national data on antibiotic prescribing in hospitals, and these do not clearly show that prescribing of broad-spectrum antimicrobials has increased; research on an association between use of proton pump inhibitors and CDI is contradictory; and there is no evidence that CDI can be transmitted from animals to humans via food.

## 2.2 Distribution and severity of *C. difficile* infection

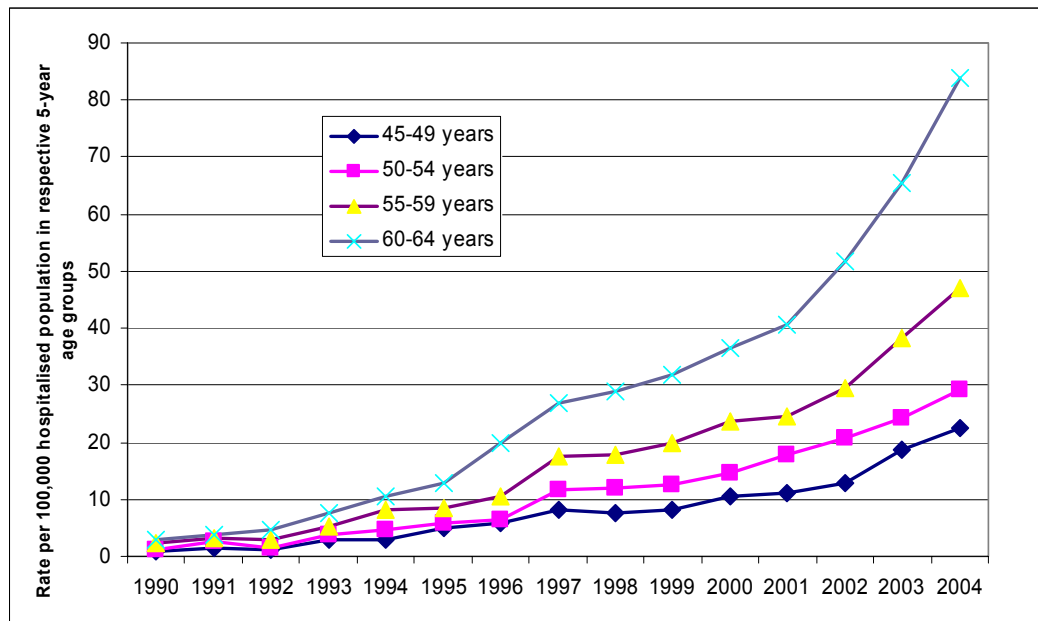
There are concerns that alongside a rise in overall incidence, CDI may be becoming more common in people previously considered at lower risk for this infection, and that the proportions of people who suffer serious complications or death may have increased. These concerns have been heightened by the increasing prevalence of *C. difficile* strains that produce greater quantities of toxin compared to “ordinary” strains (hypertoxin-producers), and reputedly cause more severe disease.

### 2.2.1 Increasing incidence in “low-risk” groups

Recent reports of CDI in groups generally considered at lower risk of CDI (for instance, children, young adults and people who had not received recent antibiotic treatment or hospital care) simply highlight the known fact that the infection does not occur only in well-known risk-groups<sup>23</sup>. More robust data on changing patterns of incidence, however, are scarce. The UK does produce some of the best available information through voluntary reporting of positive laboratory results<sup>10;24-26</sup>. This programme allows monitoring of CDI incidence in different age groups, although figures are more subject to reporting bias than the mandatory reporting scheme. Figure 4 shows how rates of the infection changed in different age groups in England between 1990 and 2004 in selected health regions. While it is apparent that the

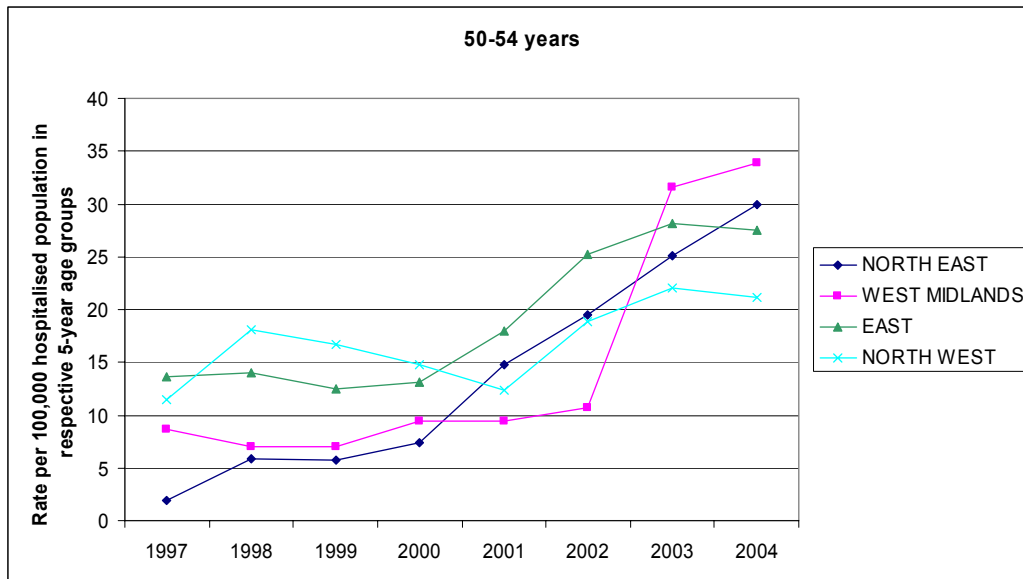
greatest increases have occurred in those in the 60-64 year age group, there have also been highly significant rises in younger people over this period ( $p < 0.001$  in all 5-year age groups). There appears to have been a gradual increase in rates in the early 1990s, followed by more pronounced increases, first around 1996-1997 and then 2001-2.

**Figure 4:** *C. difficile* rates from laboratory reports in people 45-64 years in England (excludes figures from North West, South East and London regions)

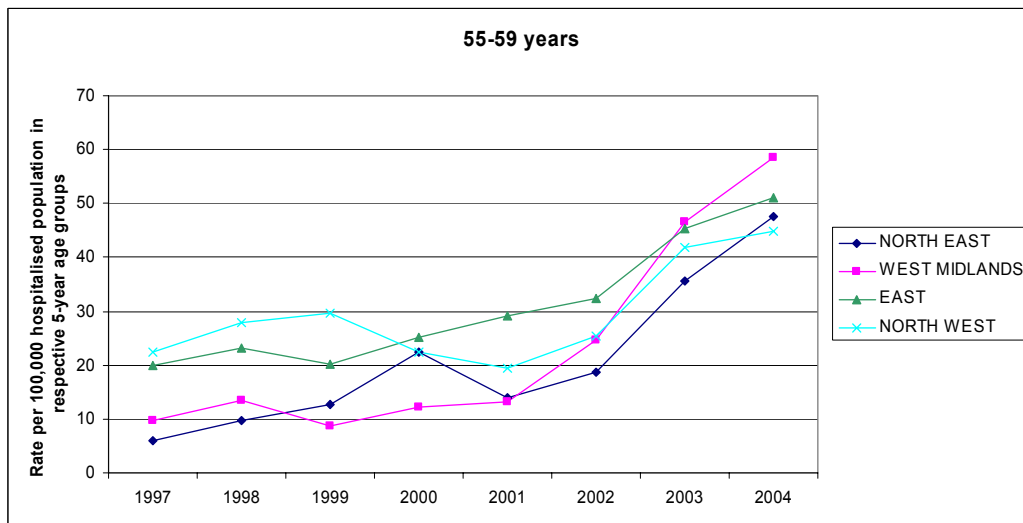


Figures 5 and 6 show changing rates of *C. difficile* in, respectively, people of 50-54 and 55-59 years. These demonstrate more clearly that the reported incidence of *C. difficile* has increased in younger age groups. Figures illustrate rates in the four regions in England with relatively consistent reporting of cases in people of 65 years and over through voluntary reporting. Therefore, it was assumed that these regions were more likely to consistently report cases in younger age groups. In these figures increases in the reported rates of CDI in the specified age groups appear to have occurred between 2000 and 2002.

**Figure 5:** *C. difficile* rates from laboratory reports in people 50-54 years 1997-2004 by region



**Figure 6:** *C. difficile* rates from laboratory reports in people 55-59 years 1997-2004 by region



To gain some idea of trusts' experience of CDI in younger age groups, the survey asked DIPCs to estimate the proportion of total cases in younger people at their trust, and whether the diagnosis was considered in children under two years old (Box 2).

## Box 2: CDI in people less than 65 years: findings from the CDI survey

Of those DIPCs responding, 47% (55/116) estimated that more than 10% of laboratory samples positive for *C. difficile* at their trust were from people less than 65 years old; 9% (11/116) estimated that more than 40% were from people under 65 years. 43% (64/150) of DIPCs stated that stools are sometimes tested for *C. difficile* from children under two years old, most commonly for diarrhoea in an immunocompromised child, persistent or antibiotic-related diarrhoea, or a specific request. This question was asked to indirectly gauge how widespread suspicion of CDI in children was. However, since *C. difficile* colonisation is widespread in children up to two years old, such testing is not recommended as it is of very limited diagnostic value.

### 2.2.2 Increasing severity of *C. difficile* infections

More severe *C. difficile* infections may result in a greater likelihood of recurrence, complications or mortality. Markers of these include: higher rates of recurrence as detected by laboratory and clinical surveillance or dedicated research studies; increased proportions of people with *C. difficile* developing complications such as pseudomembranous colitis and toxic megacolon, or requiring treatments including colectomy and admission to intensive care units; and increased numbers of death certifications in which *C. difficile* is given as an attributable or contributory cause.

Although there are difficulties in correcting for serious co-morbidities and other possible influences on outcome from CDI, existing reports do give cause for concern. In Quebec one hospital reported that the proportion of people dying within 30 days of diagnosis of CDI rose from 4.7% (8/169) in 1991-1992 to 13.8% (54/390) in 2003. During the same period the proportion suffering a complication (megacolon, perforation, colectomy, shock or death) rose from 7.1% to 18.2%. The Centre for Disease Control and Prevention, USA, has reportedly received an increasing number of reports of cases of severe *C. difficile* infection that have resulted in admissions to ICUs, colectomies and deaths<sup>6</sup>. During a prolonged outbreak of CDI in Pittsburgh, USA, between 2000 and 2001, the incidence of "life-threatening *C. difficile* infection"<sup>a</sup> rose from 0.15 to 0.34 per 100,000 accident and emergency admissions<sup>27</sup>.

In England, there are very few data suitable for evaluating whether infections with *C. difficile* are becoming, on average, more severe. The ONS report found that the

<sup>a</sup> Hypotension, tachycardia > 120/minute, tachypnoea requiring intubation and ventilation, oliguria

number of deaths with a mention of *C. difficile* was 2.3 times higher in 2004 than it was in 1999<sup>15</sup>. Age-standardised rates for deaths involving *C. difficile* in England and Wales more than doubled between 1999 and 2004, from 11.4 to 23.6 per million for males and from 10.7 per million to 23.4 per million for females. These findings may, however, reflect rising numbers of cases or an increasing propensity to mention *C. difficile* on death certificates where this was diagnosed before death, rather than an increasing case fatality rate (among deaths with a mention of *C. difficile*, the percentage in which it was the underlying cause was similar - around 55 per cent - in each year between 1999 and 2004).

### 2.3 *C. difficile* strains

To date, several hundred strains of *C. difficile* have been identified<sup>28</sup>. Nevertheless, our understanding of the epidemiological significance of individual strains is limited. Certain strains are more common in hospital patients than others and the distribution of *C. difficile* strains in the community appears to be more varied than that seen in hospitals. Strains sometimes produce different amounts of toxin *in vitro*, raising the possibility that virulence and communicability may vary. It has been demonstrated in an animal model that not all toxigenic strains are equally virulent.

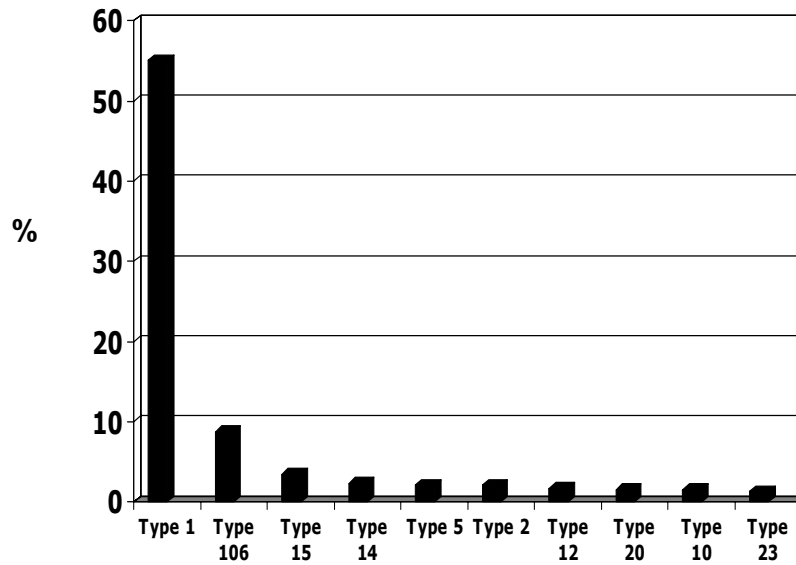
The Pittsburgh and Quebec CDI outbreaks highlighted a major current concern - that possible increases in the severity of CDI may be a result of the increasing distribution of hypertoxin-producing strains of *C. difficile*. Both outbreaks were caused by a strain of *C. difficile* which was previously responsible for only a small proportion of CDI in developed countries: Ribotype 027, also known as Toxinotype III, Nap1 and REA BI (the nomenclature is based on the method used to type it). This strain carries a binary toxin gene, and has in some laboratory experiments produced up to ten times as much cytotoxins as “normal” strains, and been associated with early and unsuppressed production of toxin. Some evidence has been published describing greater than expected mortality associated with outbreaks caused by ribotype 027, leading some to suggest that infections with ribotype 027 are particularly severe.

Data from the Anaerobic Reference Laboratory (ARL) in Wales provide us with information about the changing distribution of *C. difficile* strains, including ribotype 027, in England and Wales (data for England alone are not available). Figures 7 and 8 illustrate the proportions of cases caused by different strains of *C. difficile* strains for samples received by the ARL between 1995 and 2003. Of note, data in Figure 7 is from samples referred on specific request to the ARL for investigation of a case or

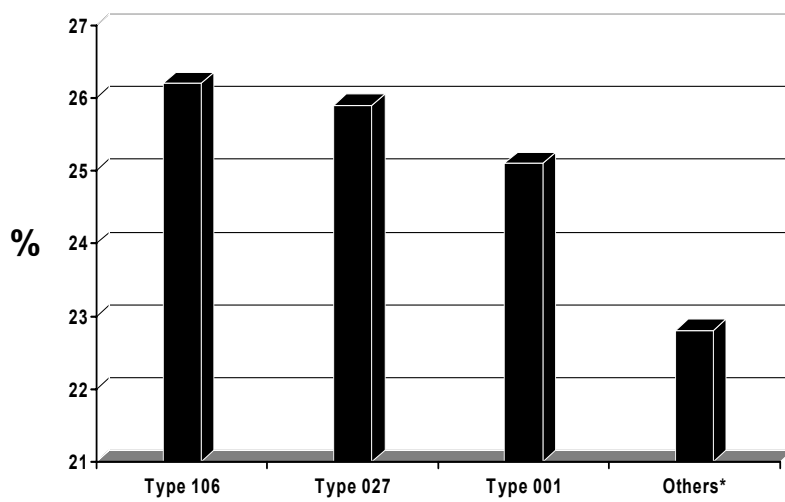
outbreak; data in Figure 8 are from samples collected through the mandatory random sampling surveillance scheme (see section 3.2), which was not available before January 2005. Therefore, the two sets of data are not strictly comparable.

Nevertheless, they show that the proportion of CDI caused by non-ribotype 1 strains appears to have increased dramatically since 1995. The proportion of cases caused by ribotype 027 has increased from less than 1% in 1995 to over 25% in 2005. We are not aware of similar data from other European or North American countries.

**Figure 7:** PCR ribotypes of *C. difficile* in hospital patients in England and Wales: from referrals to ARL 1995-2003



**Figure 8:** PCR ribotypes of *C. difficile* in hospital patients in England January-December 2005: samples from the random sampling surveillance scheme (n=881)



\* 200 isolates consisting of 22 different PCR ribotypes

Theoretically, disproportionate increases in the incidence of a *C. difficile* strain that produces ten times as much toxin as many other strains should increase the average severity of *C. difficile* infections. This hypothesis is supported by data from outbreaks in Canada and the USA<sup>16;29;30</sup>. However, anecdotal evidence from the ARL and HPA suggests that infections with type 027 are not always associated with greater mortality, and that other genomic factors play a role in determining whether particular strains cause an “average” or “severe” clinical course. Furthermore, this strain does not always produce excessive amounts of toxin when tested in vitro<sup>31</sup>.

#### 2.4 Discussion: the need for improved surveillance

There are concerns that England may be experiencing a significant change in the epidemiology of *C. difficile* infection, similar to that reported to have occurred in the USA and Canada. However, the available data are suggestive rather than confirmatory of changes in CDI epidemiology, and leave open other possible explanations.

The reported incidence of CDI in England has increased substantially between 1990 and 2005, and even more dramatically since 2001. The quantity of this increase, the consistency with which similar increases have been reported in many other countries, and the mounting anecdotal evidence of a rising disease burden, suggest that a real increase in the number of cases of CDI has occurred. Nevertheless, it is likely that

there have also been substantial increases in the detection and reporting of CDI, and the relative contributions of increasing incidence and ascertainment remain unclear.

There is some evidence that incidence has increased in groups previously considered at lower risk of CDI. This includes increasing rates of reported laboratory diagnoses in 45-64 year olds in England since 2001, and increasing rates of CDI in people under 65 years in Canada from 2002-2005. Again, however, the relative contributions of increasing incidence and ascertainment to these findings have not yet been clarified.

As in a number of other countries, an increasing proportion of cases of CDI in England appear to be due to ribotype O27. This has given rise to understandable concerns – the O27 strain has been characterised as a hypertoxin-producer, and some research from North America suggests that outbreaks of this strain are associated with increased mortality. However, although there are anecdotal reports of excess mortality due to O27 outbreaks in England, there is little evidence on wider trends in the average severity of CDI. Further, the significance of trends in the ARL data on *C. difficile* strains is unclear, since changes in the way samples have been obtained for analysis since January 2005 may have biased results by increasing the representation of cases that were not part of an outbreak. Also, the relationship between particular strains and clinical presentation has not yet been clarified. Nevertheless, the findings of an increasing numbers of death certifications mentioning *C. difficile* in England and Wales suggest an urgent need for research which would clarify this issue.

Better information than is currently available is required to accurately evaluate the concerns highlighted in this discussion. In particular, information on the incidence of CDI in people under 65 years and living in the community, trends in CDI mortality and other basic markers of clinical severity, the link between strain type and clinical severity, and research on which factors are responsible for the reported changes in CDI incidence, distribution and severity, are much needed. These information needs should probably be addressed through a combination of improved surveillance programmes and dedicated research projects.

## 2.5 Recommendations

*Existing surveillance and other information sources should be reviewed to ensure that these can adequately detect and interpret trends in CDI incidence, distribution and clinical severity.*

*There should be increased funding of research into important questions raised by recent reports and studies on the epidemiology of CDI, in particular whether:*

- *links between particular C. difficile strain types and disease severity exist;*
- *the average severity of CDI has increased;*
- *the incidence of CDI in younger age groups and the community is increasing.*

### 3. *C. difficile* surveillance activities in England

This section describes existing surveillance for *C. difficile* in England (Box 3). Information obtained from the survey on surveillance activities in acute hospitals in England is presented in boxes.

Box 3: Summary of surveillance of *C. difficile* infection in England

1. National surveillance of incidence and distribution through the:
  - a) mandatory reporting of cases in people of 65 years or older;
  - b) voluntary reporting of positive laboratory reports in people of all ages.
2. Surveillance of *C. difficile* strains through the random sampling scheme and samples sent to the ARL for outbreak investigation
3. Hospital surveillance of *C. difficile* infection
4. Outbreak reporting.

#### 3.1 Surveillance of incidence and distribution

Surveillance of incidence is most valuable when data are collected accurately, consistently and regularly; analysed data are fed back to local organisations in a timely manner; and a valid estimation of incidence is used. The survey provides information on how well existing national surveillance is succeeding in these respects.

##### 3.1.1 Surveillance of positive laboratory reports for *C. difficile*

As described in section 2.1.1, this consists of the electronic and paper reporting of all positive *C. difficile* laboratory reports to the HPA. Since it depends on voluntary participation by trusts in England, it is often called “voluntary *C. difficile* surveillance”. Box 4 describes survey findings on participation in this scheme.

Box 4: Participation in *C. difficile* voluntary surveillance

The survey found that 89% (133/150) of trusts participated in the voluntary laboratory reporting scheme. The survey did not ask particular trusts why they do not participate in voluntary surveillance. The 17 trusts who said that they did not participate included 7% (7/98) of all general acute trusts responding, 25% (5/14) of all specialist trusts responding and 36% (5/14) of all single specialty trusts responding. Of trusts not currently participating in the voluntary reporting scheme, 33% (6/18) had previously done so.

### 3.1.2 The DH mandatory *C. difficile* case reporting surveillance scheme

In January 2004, the DH introduced compulsory reporting of all cases of CDI in people of 65 years or older by all acute NHS trusts in England.

The following aspects of mandatory surveillance were covered in the CDI survey:

- accuracy of testing and reporting
- accuracy of summary measure of incidence
- information on healthcare source
- usefulness of the scheme

#### 3.1.2.1 Mandatory case reporting - accuracy of testing and reporting

Box 5 details the criteria for testing, reporting and diagnosing samples for mandatory surveillance, as recommended by the *C. difficile* Standards Group<sup>13</sup>. Adherence to these criteria is discussed in Box 6.

Box 5: Definitions and criteria for *C. difficile* testing and reporting for mandatory surveillance

***C. difficile* laboratory testing should be performed on:**

- ALL diarrhoeal specimens submitted from patients of 65 years or older who have not fulfilled the case definition of *C. difficile* infection within the preceding four weeks, regardless of whether they have been in the community or in hospital.

**Cases of *C. difficile*** are defined as:

- “all diarrhoeal specimens that test positive for *C. difficile* toxin (where the patient has not been diagnosed with *C. difficile* associated disease (CDAD) in the preceding four weeks)”.

***C. difficile* reports should be submitted for:**

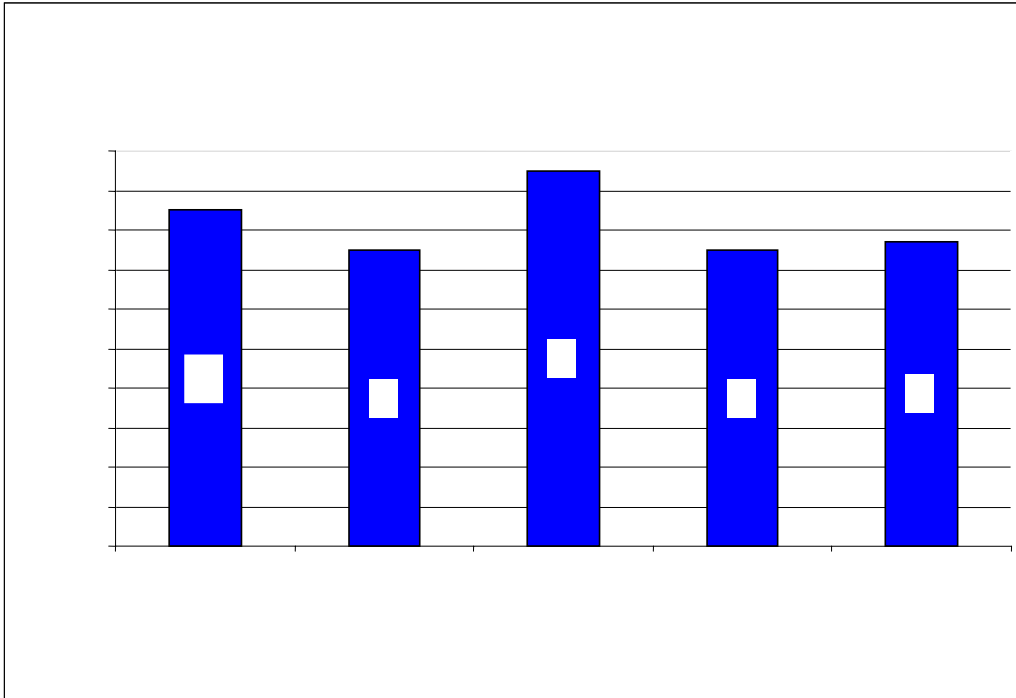
- *C. difficile* toxin positive samples detected in that acute Trust from patients aged 65 years and over who have not been diagnosed with CDAD in the preceding four weeks.
- *C. difficile* detected in samples sent to acute Trusts from community hospitals, PCT hospitals, psychiatry wards, GPs, nursing homes, other NHS-run healthcare facilities, from patients receiving independent healthcare should be reported.

#### Box 6: Survey findings - accuracy of testing and reporting for mandatory surveillance

The information that follows has been produced by combining the questionnaire responses with information from HPA regional scientists concerning their data checking practices. This is because we aimed to measure the accuracy of the national database by describing the proportions of trusts from which the HPA receives accurate mandatory surveillance data. Data received is a product of both a trust's and its regional HPA office's practice. Thus, if a particular trust's regional HPA filters mandatory surveillance data before sending these to central office, the HPA may receive accurate data even if that trust did not follow testing and reporting criteria. For example, if a trust recorded that they include samples for patients with a positive *C. difficile* result within the past 28 days but it is known that they are located in a region which 'filters out' duplicates within 28 days, then the trust's response to the question asking "do you report patients with a *C. difficile* result within 28 days?" has been altered from 'Yes' to 'No, not included'. Of note, regional filtering was strongly dependent on whether a particular region's trusts used the electronic surveillance system (rather than paper reports).

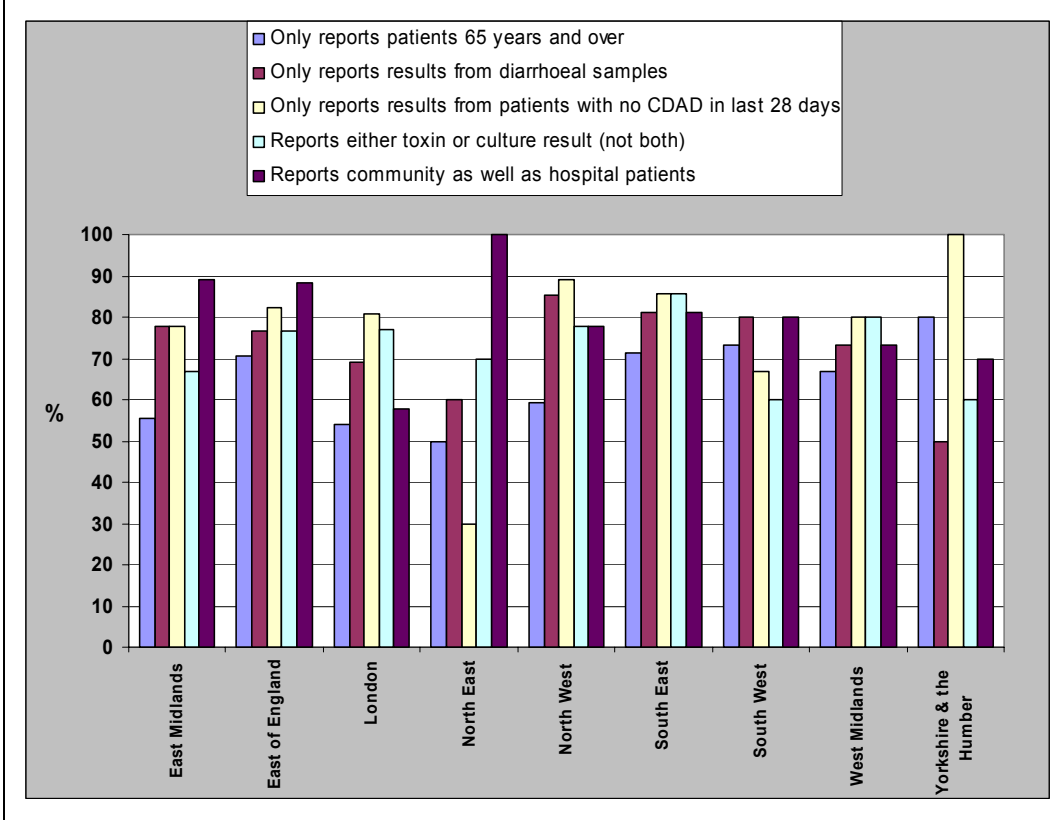
Most trusts (91%) said they were clear about the existing criteria for mandatory testing and reporting of *C. difficile* samples and cases. However, subsequent responses indicated that substantial numbers were not following guidelines. For example, over 20% of DIPCs said that their trusts test non-diarrhoeal samples, 34% did not test community samples, up to 15% report cases from people under 65 years, and 23% did not report community cases. These results are shown in Table 1, Appendix 2, which summarises adherence to criteria for testing samples, and Tables 2 and 3 in Appendix 2, which summarise adherence to criteria for reporting cases of CDI.

The proportions of trusts correctly following selected criteria are shown in Figure 9.



There were no significant differences in adherence to mandatory surveillance guidelines criteria according to either type of trust or incidence of *C. difficile*. Figure 10 shows adherence to the mandatory reporting scheme criteria grouped according to region.

**Figure 10: Adherence to mandatory surveillance criteria by region (England)**



**3.1.2.2 Mandatory case reporting - validity of trust incidence measure**

Currently, incidence of CDI at different trusts is expressed as the number of reported cases in people of 65 years and over divided by the number of bed days for people of 65 years and over in the particular acute trust. Acute NHS Trusts are required to report all stool samples positive for *C. difficile* processed by their laboratories, including those thought to have been acquired in the community. Trusts CDI incidence rates are calculated by dividing the number of *C. difficile* reports in people aged 65 years and over for the time period x 1000, by the total number of bed-days for patients aged 65 years and over for the time period. The denominator does not include a measure of people of 65 years and over in the community because it was presumed that cases of community-acquired CDI would account for only small proportion of a trust's cases, and this small proportion did not justify the effort involved in obtaining a denominator representing both community and hospital patients. Anecdotally there are concerns that the proportion of cases acquired in the community is greater than expected in some areas. Consequently, the survey asked DIPCs what they thought the proportion of cases requested from community sources was, and what denominator they believed would be the most appropriate for *C. difficile* mandatory surveillance, assuming that it was possible to separately report

community hospital cases. For the latter question, five options were offered. Responses are shown in Box 7.

Box 7: Survey findings - validity of trust incidence from mandatory surveillance

Of those who responded, 50% of DIPCs reported that at least 6% of positive *C. difficile* samples were requested by general practitioners, and 36% said that at least 6% were from community hospitals. It is not known whether these might have been previously acquired in an acute hospital.

In the survey, the clear preference was for using separate denominators for acute trust and community hospital cases (Table 4, Appendix 2). We then asked DIPCs whether they were currently able to provide accurate denominator and numerator data for the option they had chosen. Of those responding 48% (65/136) said yes, 24% (33/136) said no, and 28% (38/136) said they did not know.

3.1.2.3 Mandatory case reporting - information on healthcare source

To explore possibilities for improving current data collection and reporting, the survey asked DIPCs what information their laboratories currently collect on the healthcare source of specimens submitted for *C. difficile* analysis. The Standards Group did recommend that trusts provide information on the healthcare source of positive specimens reported in mandatory surveillance, the original aim being to distinguish between hospital and community-acquired cases. Box 8 summarise findings from the survey.

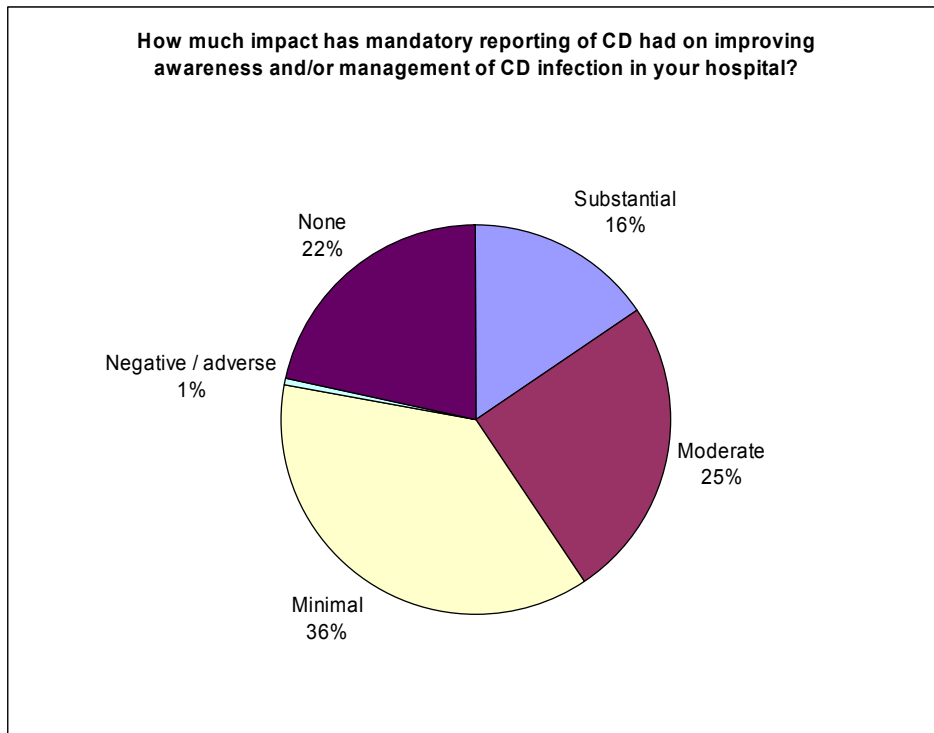
Box 8: Survey findings - information on healthcare source for mandatory surveillance

Many trusts also collect information on healthcare source (Tables 5 and 6 in Appendix 2). Most of these stated that they would also be easily to able identify patients from these sources for reporting purposes; for instance 103/134 (77%) said they would be able to identify if samples had been requested on patients from community hospitals. Nevertheless, substantial numbers of trusts either do not collect or would be unable to supply these data, especially for patients from nursing or residential homes, private care facilities or other trusts. In particular, a number of respondents commented that it was difficult to distinguish between requests on patients in private care facilities and patients in nursing or residential homes.

### 3.1.2.4 Views on the usefulness of mandatory case reporting scheme

Mandatory surveillance provides more robust national data on *C. difficile* and allows inter-hospital comparisons. DIPCs have found it less useful for the local management of *C. difficile* (Figure 11) where additional local information on affected units etc is required. This was further reflected in many DIPCs' comments on the difficulty of interpreting local incidence figures derived from mandatory surveillance (Box 1 in Appendix 2).

**Figure 11:** DIPCs views on the usefulness of the mandatory reporting scheme



### 3.2 Surveillance of *C. difficile* strains - the Random Sampling Scheme

The Random Sampling Scheme forms part of the mandatory surveillance of *C. difficile* and was implemented nationally on 1<sup>st</sup> January 2005. The numbers of specimens being referred to the ARL in Cardiff had dwindled over recent years, so that there was little information on whether prevalent strains and antimicrobial susceptibilities were changing. The scheme was introduced to obtain more information on:

- which *C. difficile* strains are prevalent in England;
- what proportion of *C. difficile* cases are caused by each of these strains;
- trends in the proportion of cases in England caused by particular strains;
- the susceptibility of *C. difficile* strains to specific antibiotics

Acute trusts in England are required to submit *C. difficile* samples to the ARL in accordance with a national sampling schedule. Every 12 months, each acute trust is randomly allocated one week for random sampling. During that week, trusts should provide consecutive positive *C. difficile* samples (excluding multiple specimens from an outbreak) received in their laboratory up to a maximum of ten. Following culture at local or regional level, *C. difficile* isolates are sent to the ARL. Strains are identified through a genomic analysis of intergenic spacer regions between 16S - 23S rDNA using a technique known as PCR ribotyping. Results of the sampling scheme are sent back to the relevant regional laboratory once the region has completed its schedule. However, unusual or untoward results, including detection of PCR ribotype 027, are fed back immediately, without waiting until the completion of the schedule. The results for a full year of the routine sampling scheme will be available in July 2006.

Box 9: Survey findings on the random sampling scheme

The survey aimed to find out how widespread is knowledge of and participation in the random sampling scheme. We found that 77% of trusts have or are planning to participate. There is still confusion about the programme's status: only 47% of respondents thought that it was mandatory, 32% thought it was voluntary, and 21% were unsure.

3.3 Hospital surveillance of *C. difficile* infection

It is recognised good practice that all Trusts should undertake 'alert organism' surveillance, which includes surveillance of *C. difficile*<sup>32</sup>. The survey aimed to discover how widespread this was and what forms it took (Box 10).

#### Box 10: Local surveillance for *C. difficile* in England

The great majority of DIPCs confirmed that some form of local surveillance is undertaken (93% or 140/150 respondents). For the purposes of analysis, we classified the forms of surveillance performed by trusts into eight types of activity (Table 7 in Appendix 2). These were not mutually exclusive and many or most trusts' responses could be classified as falling into more than one type of activity. The most common forms were regular review of cases, and a local database of cases (30%), including records of the ward or specialty where the case was diagnosed (28%).

"Other" forms of surveillance included:

- daily or weekly testing of specimens from patients on high risk units;
- regular clinical audit in high risk areas e.g. elderly care units;
- recording information on probable source of infection;
- questionnaire surveys of clinicians;
- use of surveillance software;
- analyses of clusters or outbreaks of cases.

18 trusts (12%) mentioned reporting of "alert organisms" to the HPA (as part of national hospital infection surveillance)<sup>32</sup>.

We also asked DIPCs what type of additional information they had found useful in managing cases or outbreaks of *C. difficile* (Table 8 in Appendix 2). The most frequently cited was information on antimicrobial prescribing. Many of the responses were similar to those for local surveillance. Other information said to have been useful included root cause analysis, strain typing, bed occupancy rates and availability of side rooms, use of Bristol Stool Charts to maintain consistent reporting of cases, analysis of patterns of patient isolation and movement in hospital, protocols with criteria for using immunoglobulin in cases with relapse or re-infection, and expert advice.

In Canada, one of the first signs that a new and potentially hypervirulent strain of *C. difficile* had appeared was a localised increase in the clinical severity of *C. difficile* infection<sup>16;17;30</sup>. Therefore, we wanted to explore the possibility of obtaining surveillance information on this and were interested in what data trusts currently collect on clinical severity. As highlighted above, only 6/150 (4%) of trusts said they routinely collect data which could be used to monitor clinical severity directly. Furthermore, only 11 (7%) said that they had used information on clinical severity

during management of *C. difficile* outbreaks. When asked more specifically about information collected, the proportions of DIPCs who reported that their trusts would be easily able to provide data that could be used to monitor clinical severity in all patients with *C. difficile* were, respectively, 17% (length of illness), 23% (whether patient had severe or complicated disease), 20% (whether colectomy was performed), 40% (information on whether disease was relapsing), and 29% (information on whether patients had died). Where data were available, these were usually collected by infection control clinicians as part of an outbreak investigation. Responders stressed that they were less likely to retrieve paper records than those in an electronic database. Several trusts commented on the lack of resources available to collect data on clinical severity.

### 3.4 Outbreak reporting

Effective and timely intervention during *C. difficile* outbreaks is critically important in controlling the spread of this infection. Outbreaks need to be detected and reported if they are to be managed effectively: detection is a trigger for the implementation of appropriate control measures; reporting allows recognition of changes in local and national disease patterns, and facilitates appropriate quality control processes to ensure that all necessary measures have been implemented and dissemination of lessons learnt.

One of the biggest obstacles to these tasks is the difficulty in agreeing a clear definition of what circumstances represent a *C. difficile* outbreak. Detection of new outbreaks of *C. difficile* can be difficult where high or continuously rising numbers of cases have become the norm. For this reason existing definitions usually emphasise the need to take account of the background rate of infections locally; for example, the *Clostridium difficile* Standards Group recommended that outbreaks should be defined as the “*occurrence of two or more related cases over a defined period taking account of the background rate*”<sup>13</sup>. The survey found that use of this definition to define local outbreaks is variable (Box 11).

The *Clostridium difficile* Standards Group also recommended that suspected outbreaks or clusters of CDI should be reported to Regional Communicable Disease Surveillance Centres, now Regional Epidemiologists or Consultants in Communicable Disease Control<sup>13</sup>. The survey found that adherence to this recommendation is neither comprehensive nor consistent (Box 11).

#### Box 11: Findings from the CDI survey - outbreak reporting

When asked for their definition of a *C. difficile* outbreak, DIPCs' responses varied widely in terms of the numbers of cases and the methods of deciding whether cases were linked in time and space. None of the definitions specifically mentioned the local background rate, though this may have been implicit in the reported definitions. No trusts gave an indication of how the definition might change if their local background incidence altered.

The *Clostridium difficile* Standards Group also recommended that suspected outbreaks of *C. difficile* should be reported to appropriate authorities, particularly Regional Epidemiologists or CsCDC. The survey found that adherence to this recommendation is neither comprehensive nor consistent. The proportions of trusts "always", "sometimes" and "never" reporting *C. difficile* outbreaks to the HPA, NHS and independent authorities are shown in Table 9 in Appendix 2. What is evident is that many trusts do not report outbreaks to the HPA; several never do so. Despite this low reporting, almost half (72/150 or 49%) of trusts had held local investigations into an excess of cases or outbreak of CDI during 2004–2005.

Mechanisms for reporting *C. difficile* outbreaks as serious untoward incidents may also not be working, since a small proportion of trusts said they inform Strategic Health Authorities, and only three foundation trusts said that they have informed *Monitor* (their regulator) of a *C. difficile* outbreak, although more will have experienced outbreaks.

#### 3.5 Discussion: the adequacy of current surveillance of CDI in England

Ideally, surveillance should monitor the impact of *C. difficile* by accurately recording trends in incidence and clinical severity, recognising the emergence of new strains or changes in the frequency of infection with particular strains, and permitting detection of outbreaks. Information should be obtained without placing an excessive burden of work on those collecting and processing data, and should be publicised in a timely manner. Current CDI surveillance schemes in England are designed to monitor incidence, geographic distribution (and to a lesser extent age distribution), the prevalence of different strains, and the occurrence of outbreaks. There is no national surveillance of average clinical severity of CDI, nor of the links between different *C. difficile* strains and clinical severity.

### 3.5.1 Surveillance of incidence

Although participation in voluntary surveillance is widespread, it is notable that the proportion of specialist and single specialty trusts which do not participate is substantial, and far exceeds that for general acute trusts. Of note, specialist trusts show the highest rates of CDI in *mandatory* surveillance in 2004 (individual trust CDI rates are not produced from voluntary surveillance). Therefore, it is possible that trusts with some of the highest numbers of *C. difficile* infections do not participate in voluntary surveillance. This obviously diminishes the completeness of this surveillance programme. Completeness is also been hampered by under-reporting of laboratory cases from particular areas. Incomplete coverage is particularly regrettable since voluntary surveillance is the only national programme which obtains data on *C. difficile* incidence in all age groups.

The survey highlights a number of possible problems with the mandatory *C. difficile* case reporting scheme. First, adherence to the Standards Group's criteria for testing and reporting of stool samples for *C. difficile* on people over 65 years is inconsistent. This affects the accuracy of individual trust, regional and national rates of CDI in people over 65 years, and the reliability of comparative data.

Second, the reporting of CDI cases thought to have been acquired outside the reporting trust, particularly in the community, is controversial. Anecdotally, many DIPCs believe that community cases comprise a higher proportion of total cases than predicted, and that this proportion is likely to vary between trusts. It is argued that these cases unfairly distort trusts' CDI incidence rates, particularly those whose laboratories process and report on greater than average proportions of samples received from community healthcare sources. This would invalidate comparisons of rates between different trusts. Also, most DIPCs had not found mandatory surveillance useful for local prevention and control of CDI.

It should be noted that mandatory surveillance was introduced to provide more robust national data on CDI incidence and to allow inter-hospital comparisons. Therefore, it was important that community as well as acute hospital cases should be reported. It is not surprising that DIPCs have found the scheme less useful for the local management of CDI, for which additional local information is required. Nevertheless, trusts' concerns about incidence are understandable, since it is perhaps inevitable that publication of trusts rates will result in judgements being made about local infection control practices and healthcare quality.

Systematic data on the proportion of mandatory surveillance cases from different settings are scarce since trusts do not routinely provide information on the healthcare source of cases reported, even though this was specifically recommended by the Standards Group. A starting point for improving our understanding and reflection of community versus acute hospital cases would be for trusts to start reporting information on the healthcare source of cases as required, and there is evidence from the survey that many would be easily able to provide these data. Although previous research did indicate that the impact on trust incidence of community CDI cases was likely to be minor, this should probably be reviewed, possibly through a dedicated research study or pilot. This could indicate whether distinguishing community from hospital-acquired cases in trust incidence rates is necessary, and provide valuable information on the distribution of CDI in the community.

However, this will not solve the inherent problem in defining what should be regarded as a community case, particularly where cases are admitted with CDI following recent discharge from hospital. Definitions of these, and quality control processes for ensuring adherence to these definitions, would be needed to make mandatory surveillance data more fairly representative of trust incidence, but still reflective of the overall national incidence of CDI in people over 65 years.

In summary, there are currently two surveillance systems for monitoring CDI incidence in place, the original voluntary reporting system and the more recent mandatory surveillance. They have different strengths and weaknesses, for instance, the voluntary system includes individual episodes of infection, with information on age, sex and antimicrobial prescribing, but does not ensure comprehensive coverage or diagnostic consistency; the mandatory system brings in greater participation, but is essentially total numbers of infections in the over-65s.

Overall, there is room for improving four main aspects of these surveillance schemes:

- accuracy (the most important factor probably being improving adherence to criteria for testing and reporting stool samples for mandatory case reporting);
- completeness (increasing the proportion of trusts reporting to the voluntary scheme; more generally, improving reporting of CDI in people under 65 years)
- descriptiveness (primarily improving submission of healthcare source data; also, obtaining data on risk factors for CDI, particularly antimicrobial prescribing);

- comparability (ensuring that methods of obtaining trust and regional incidence are fair, including addressing the possible impact of community and independent sector cases on these rates).

It would be sensible to amalgamate the strengths of both systems to achieve these without duplicating effort – methods for doing so should be considered.

### 3.5.2 Surveillance of *C. difficile* strains

Surveillance of *C. difficile* strains should allow recognition of the emergence of new *C. difficile* strains or changes in the frequency of known strains. The random sampling scheme has already provided interesting data on the changing distribution of particular *C. difficile* strains in England. As intended, the programme has provided a picture of *C. difficile* strain distribution across most of England - participation has been good after a slow start (although awareness of the scheme's status is incomplete). However, there is still much uncertainty about the implications of the random sampling scheme's findings for local, regional and national management, prevention and control of CDI. Furthermore, although broadening the geographic range from which isolates are obtained has enhanced the ARL's ability for early detection of new *C. difficile* strains, these may still be missed. For instance, ten samples may be poorly representative of trusts with over 500 cases per year, and strains may appear in areas which have already completed their annual sampling.

It may well be unwise to abandon an established scheme that many European countries are planning to implement, whose future benefits are hard to foresee, which is not particularly onerous (trusts are only required to send off 10 samples once a year), and whose discontinuation soon after its introduction would make any re-introduction difficult should the need arise in the future. However, the random sampling scheme's continued usefulness probably depends on better elucidation of the links between strains and clinical patterns. The need for continuous sampling and the number of samples needed to adequately appraise prevalence of different strains in a trust or region should probably also be reviewed. In addition, the fact that strains may first appear in other countries suggests the need to strengthen international networks for monitoring or communicating information on the appearance of new strains, or changes in the prevalence of known strains.

### 3.5.3 Surveillance of clinical severity

Infections present a greater public health threat when they are more likely to cause a severe illness including death. Therefore, information on trends in the average severity of CDI can help in evaluating whether current infection control strategies are appropriate to the magnitude of the public health threat. In addition, if it were shown that certain strains of *C. difficile* were associated with unusually severe disease, local information on changing severity may alert infection control professionals to the presence of particular strains in their hospitals or areas.

At present, there are very few systematic data on trends in the clinical severity for CDI in England. The joint ONS/HPA study described can at best provide circumstantial information on possible changes in clinical severity, and local surveillance in English trusts is very uncommon. Should the evidence suggest there is value in obtaining systematic surveillance data to monitor changes in the average clinical severity of CDI, this would need to be carefully balanced against the considerable difficulties and resource implications of doing so. Markers of severity have never been part of a national CDI surveillance scheme. Although clinical and laboratory markers of severe CDI have been identified<sup>b</sup>, the latter are probably not suitable for routine surveillance. It may be easier and cheaper to obtain information through research or pilot studies, or via network or regionally collected data.

Perhaps the most cogent additional aspect to surveillance would be the collection of data on antimicrobial prescribing as this is one of the main risk factors for the development of *C. difficile* infection. National surveillance on antimicrobial prescribing in hospitals would provide much-needed focus and help to promote the vital role of effective and monitored antimicrobial management in infection prevention and control.

### 3.5.4 Surveillance of outbreaks

The survey found that the Standards Group's recommendations on defining and reporting outbreaks are either not widely understood, or being ignored. Both definitions and practices for reporting CDI outbreaks are inconsistent. Our finding that less than half of all responding trusts have performed an outbreak investigation during the past 12 months indicates that outbreaks are not being recognised (as recent evidence suggests that outbreaks are more widespread), investigated or

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<sup>b</sup> *Clinical*: death within 30 days of diagnosis, colectomy, shock, megacolon, bowel perforation;  
*Laboratory*: high white cell counts ( $>20,000/\text{mm}^3$ ), raised creatinine ( $>200 \mu\text{mol/l}$ ), increased peak lactate levels ( $>5.0 \text{ mmol/l}$ )

reported. As further evidence of under-reporting, only 16 CDI outbreaks were reported to the HPA in 2004, a year with over 40,000 reports of *C. difficile*.

Overall, there is an urgent need to improve the reporting of *C. difficile* outbreaks in England. Unrecognised outbreaks cannot be investigated to obtain epidemiologic or laboratory evidence of links between cases, while unreported outbreaks provide no external mechanisms for checking whether further assistance to contain the outbreak is required or collating information on lessons learnt for wider dissemination. However, the perception that reporting will bring no clear benefits to trusts, only greater critical scrutiny, makes it difficult to change reporting practices. Anecdotally, there is a view that outbreak situations do not require a change in approach if prevention and control measures are already being implemented. This ignores the likelihood that in many hospitals with endemic rates of CDI there is likely to be room for improvement, and outbreaks can provide a critical spur for doing so. In addition, it can be argued that any outbreak represents a failure of prevention measures, and a persisting outbreak a failure of control. Nevertheless, it seems reasonable that existing definitions of a CDI outbreak should be reviewed, particularly with respect to their practical value in identifying early outbreaks in situations where CDI is hyperendemic. Whether better reporting of CDI outbreaks simply requires efforts to improve compliance with existing recommendations, or modification of these recommendations, should also be considered.

### 3.6 Recommendations

1. *Consideration should be given to addressing the following aspects of current national surveillance of C. difficile incidence:*

- *Amalgamating the strengths of the voluntary and mandatory C. difficile incidence surveillance systems to avoid duplication of effort.*
- *Ensuring a consistent approach nationally to the*
  - *Diagnosis of infection*
  - *Reporting of cases*
  - *Reporting of healthcare source*
  - *Definition of outbreaks and hyperendemic situations*
  - *Reporting of outbreaks*

*This requires consideration of current recommendations, whether they need to be updated or reiterated, and how best to deal with the issues of community-acquisition, severity of infection and risk factors. Should these be addressed through surveillance or is there a more practical approach?*

*There is a need to identify the impact of community cases on CDI disease burden – how important is it to distinguish these in routine surveillance?*

2. *The following aspects of C. difficile strain surveillance should be reviewed:*
  - *The continuing objectives of the random sampling programme, in order to make recommendations on its future development.*
  - *The need to strengthen international networks for monitoring or communicating information on the appearance of new strains, or changes in the prevalence of known strains.*
3. *Consideration should be given to obtaining data to monitor trends in the clinical severity of CDI, but this should be balanced against the practical difficulties of collecting such data. This may be best addressed in a dedicated research project or pilot.*
4. *Consideration should be given to introducing surveillance of risk factors for CDI, particularly national monitoring of antimicrobial prescribing.*

#### 4. Laboratory practice for *C. difficile*

Laboratory investigation of suspected *C. difficile* infection includes tests to diagnose infection, culture the organism, and identify the particular strain causing disease.

##### 4.1 Diagnostic tests for *C. difficile*

The *Clostridium difficile* Standards Group recommended that laboratories should test specimens for *C. difficile* toxin using either an immunoassay detecting both toxin A and toxin B, or a neutralised cytotoxicity assay<sup>13</sup>. Box 12 describes findings from the survey on diagnostic tests for CDI.

Box 12: Diagnostic tests for *C. difficile*: findings from the survey

94% (141/150) of trusts said that their laboratories process samples submitted for *C. difficile* investigation. The majority of these carry out diagnostic toxin tests only. The survey showed that 99% (140/141) of laboratories are using one of these tests. This confirms improvements in laboratories' practices compared to a survey in 2002.

The most commonly used criteria for deciding whether a sample from a person under 65 years should be tested were, in order, a subjective assessment, a specific request, healthcare setting, and prior antibiotic therapy; absence of other known pathogens was rarely cited. The likelihood of respondents saying their trust used any of these criteria was not statistically related to the type of trust (specialist, single specialty or district general hospital trust) or CDI ranking (based on the first year of mandatory *C. difficile* surveillance).

Almost all trusts said that their laboratories used a protocol for processing samples for diagnosis of *C. difficile*; 79% of those who responded had used a national guideline for their protocol, 19% had used local guidelines, and 2% had used both national and local guidelines. Nevertheless, in contravention of national recommendations on diagnosis in people over 65 years (as discussed in section 3.1.2), 14% (21/150) of trust respondents said they did not test all diarrhoeal samples, 24% (31/131) did not test samples from patients in the community, and 19% (28/150) tested non-diarrhoeal samples.

#### 4.2 C. difficile culture and strain identification

The diagnosis of *C. difficile* infection is normally by toxin detection and does not require culture of the organism. Positive culture by itself does not necessarily mean an infection is present (*C. difficile* may be passing through the gut as a spore and/or a non-toxicogenic strain). However, culture is necessary if further investigations are to be undertaken on the specimen, for instance, identification of its epidemiological type and antimicrobial susceptibilities. Epidemiological typing assists in the investigation of possible outbreaks, to identify whether cases are likely to be linked. In addition, culture sometimes helps in toxin detection. Boxes 13 and 14 detail survey findings on trusts' use of culture and strain identification, respectively.

##### Box 13: *C. difficile* culture: findings from the survey

Only 25% (37/146) of trusts reported that their laboratories perform *C. difficile* culture; 18% (26/146) said that their laboratories send samples elsewhere for culture, and 56% (82/146) neither perform nor send samples elsewhere for culture; 27 trusts (18/150) said that their laboratories are considering introducing *C. difficile* culture. Teaching hospitals (30%) were slightly more likely than general acute trusts to have culture facilities (23%).

The most commonly cited reason for performing culture was occurrence of an outbreak, followed by investigating patients with a severe or complicated course, and those who had failed to respond to treatment. Only 8/150 (5%) said they would consider requesting *C. difficile* culture on a suspected case whose stool sample was toxin negative. 47% of trust respondents said that their laboratory had a protocol with criteria for selecting faecal specimens for culture. Roughly equivalent numbers of trusts who responded had used national or local guidelines to inform these protocols.

##### Box 14: Identification of *C. difficile* strains: findings from the survey

47% (70/150) of trusts said that they had requested typing to aid management of a *C. difficile* outbreak. 27% (17/62) of those who responded said they had found strain identification results useful.

#### 4.3 Discussion: ensuring a rational approach to *C. difficile* laboratory testing

##### Diagnostic tests for *C. difficile*

The survey confirmed that use of recommended diagnostic tests for *C. difficile* based on testing for toxins A and B is almost universal, a substantial improvement on the situation in 2002. However, two issues suggest that existing diagnostic

recommendations may not be appropriate in all situations. First, there is evidence that some kit toxin assay methods have the potential for higher false positive results than previously supposed<sup>33</sup>. Second, recent research suggests that toxin tests may not diagnose a proportion of cases (up to 3.4%)<sup>34</sup>. Since many of these may have been detected by culturing the organism and determining the toxigenic status of the organism, some have suggested that stool culture should be considered if toxin tests are negative, but CDI is strongly suspected on clinical grounds.

#### C. difficile culture and typing

Overall, routine use of culture varies considerably throughout Europe, with more than 90% of the laboratories in Denmark and Belgium performing it, but only 28% in Spain and 25% in England<sup>34</sup>. The survey found that availability and use of culture in acute hospital trusts varied. Since these figures are remarkably similar to those found in a previous survey, use of *C. difficile* culture in England does not appear to have changed much since 2002. Survey findings may have been due partly to some DIPCs' lack of awareness of the availability of certain laboratory techniques, particularly those who work at trusts which refer all samples for *C. difficile* testing to other trusts, and those who relied on others for information about laboratory processes. This is suggested by the high proportion of trust respondents who said they neither performed nor ordered *C. difficile* culture, despite a much higher proportion saying that they did participate in random sampling. Findings may also indicate that many DIPCs and others involved in infection management, prevention and control are unconvinced of the value of requesting *C. difficile* culture.

Less than half of all trusts said that they had requested *C. difficile* strain identification tests and a relatively small proportion had found these useful. Overall, findings from the survey suggest the need for clear recommendations on use of CDI culture and strain identification.

#### 4.4 Recommendations

1. *Guidelines on the use of C. difficile culture and strain identification should be reviewed and disseminated.*
2. *Laboratory methods for detecting C. difficile should be reviewed and the literature critically appraised to ascertain the accuracy and reliability of currently recommended diagnostic tests for C. difficile.*

## 5. Prevention and control of *C. difficile* infection

This section discusses recommendations for prevention and control of *C. difficile* infections, and evidence from the survey on adherence to these at acute Trusts in England. It does not consider treatment of individual cases of *C. difficile*, including the management of relapsing and severe disease.

### 5.1. Existing guidance on *C. difficile* infection prevention and control

Recommendations for the prevention and control of *C. difficile* have not changed substantially since the joint DH PHLS Report on *Clostridium difficile* prevention and Management in 1994<sup>20</sup>. A literature review which formed part of the *Clostridium difficile* Standards Group's Report to the DH in 2002 concluded that practices known to reduce the incidence of *C. difficile* fell into two categories: infection control practices, including good hand hygiene, environmental cleaning and isolation of patients with existing disease; and antimicrobial manipulations. The Group reiterated recommendations from the 1994 guidance for promoting these practices<sup>13</sup>.

### 5.2 Evidence on current prevention and control of CDI at acute trusts in England

The final section of the survey addressed trusts' practices for preventing and controlling CDI. Most questions focused on specific areas of prevention and control (Boxes 15 and 16), but DIPCs were also given an opportunity to express their broader views on this subject (Box 17).

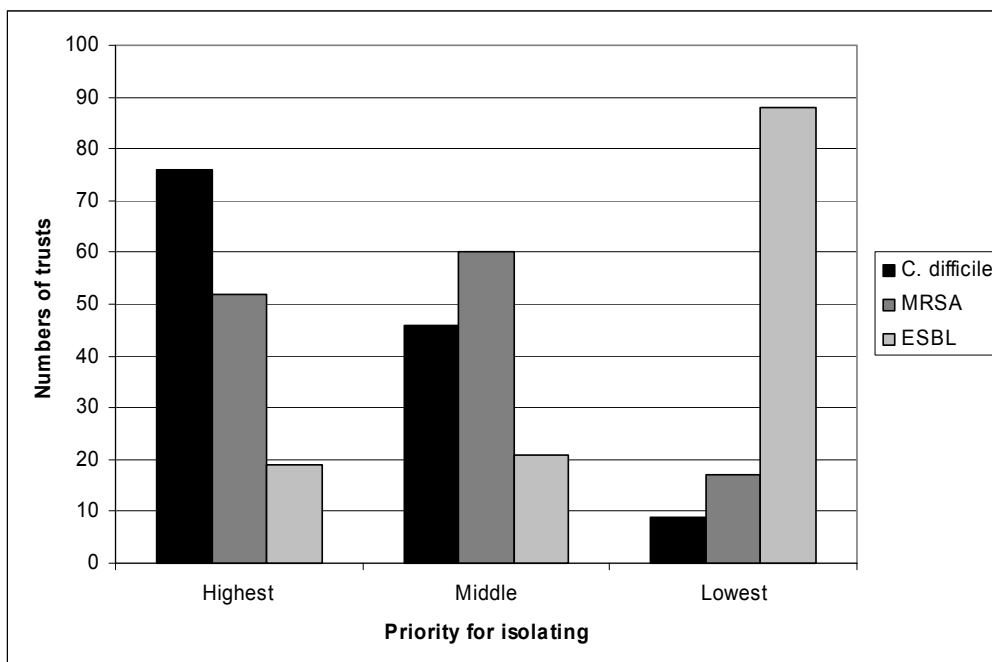
#### Box 15: Policies for *C. difficile* prevention and control

91% (136/150) of trusts said that they had a written control policy which covered management of cases of *C. difficile*. 77% (115/150) said that they had a written control policy which covered management of outbreaks of *C. difficile*, though some of those who did not have such a policy said that other policies (e.g. gastrointestinal disease policies) covered this area. Table 10 in Appendix 2 shows the frequency with which *C. difficile* policies covered major areas for infection control. Of note, 79% (119/150) of trusts had policies recommending good antibiotic practice, but a lower proportion (63% or 95/150) said they had policies for restricting use of broad spectrum antibiotics.

## Box 16: Implementation & monitoring of CDI prevention and control measures

97% (146/150) of DIPCs said that hand washing was audited at their trusts. 76% (114/150) said that their trust audits antibiotic prescribing. 65% (97/150) of trusts said that they had restricted use of antibiotics as an intervention for *C. difficile* control. Overall, infections with *C. difficile* were considered the highest priority for isolation when compared to MRSA and bacteria carrying Extended Spectrum Beta Lactamases (ESBLs) infections (Figure 12).

**Figure 12:** Priority trusts would give to isolating cases of *C. difficile*, MRSA and ESBL



Although most trusts do isolate cases of *C. difficile* routinely, substantial numbers (56/149 or 38% of responders) do not (Table 11 in Appendix 2). Only 11% (16/150) of trusts said that they have a ward which can be used for isolating patients with *C. difficile*, and only 26/150 (39%) of trusts had closed a ward due to CDI in the 12 months preceding the survey. The latter is a surprisingly small proportion given the numbers of trusts reporting large numbers of cases through mandatory *C. difficile* surveillance – in 2005, 144/173 trusts reported more than 100 cases of *C. difficile*. There were no statistical associations between either trust type or trust rank for *C. difficile* incidence and a positive response to questions about:

- antibiotic restriction measures
- performance of antibiotic audit
- presence of a ward for isolating patients with *C. difficile*
- “routine” isolation of cases of *C. difficile*

Box 17: Views of DIPCs on measures to reduce impact of CDI

DIPCs were asked what they believed were the most practical measures that could be taken to reduce the impact of CDI in their trusts. The great majority of their responses fell into one of the following categories:

- Effective and monitored antibiotic management (92 comments)
- Increase number of isolation facilities in hospitals (57 comments)
- Maintain better cleaning levels/increase cleaning schedules (52 comments)
- Improve hand washing with soap and water when caring for patients with diarrhoea (30 comments)
- Improve professional and public education/awareness (18 comments)
- Increase staffing levels (14 comments)
- Reduce bed occupancy (14 comments)

Other categories of comment included:

- Suggestions for using enhanced surveillance of CDI cases for prompt feedback on status to ward staff and infection control teams (7 comments)
- Establishing a dedicated “diarrhoea and vomiting” team
- Comments that further measures were either unnecessary or likely to be futile, for example:

“Keep going as we are.”

“We are doing all we can.”

“I do not believe further reduction in our CDI rate is realistic - our hospital already has the lowest rate of CDI in our region, and we rarely experience CDI outbreaks. With an increasing ageing hospital population, the CDI rate is likely to increase in the long term.”

Of the small number of trusts (16/150 or 11%) that had recorded a decrease in infections from *C. difficile*, 15 (92%) stated that they believed that this was due partly or wholly to improved control of antibiotic prescribing. Over two thirds of the trusts thought that the prescribing of antibiotics and the lack of facilities for isolation represented the greatest challenges to controlling infections. High numbers of both admissions and transfers of patients were cited by 28% of trusts.

### 5.3 Discussion: improving the prevention and control of *C. difficile*

Increases in the incidence and distribution of CDI suggest that current measures to prevent and control CDI are inadequate. This raises the question of whether the problem is insufficient implementation of current guidelines on prevention and control, or a need to review these guidelines.

#### 5.3.1 Inadequate implementation of guidelines on prevention and control

The survey found considerable evidence of non-compliance with existing recommendations on prevention and control. Almost 40% of DIPCs said that their trusts do not routinely isolate cases of *C. difficile*. Substantial numbers of trusts did not report having a written policy on the management of outbreaks of *C. difficile*. Although several who did not said that this was appropriately covered in other policies (e.g. infectious diarrhoea policies), these may not be specifically tailored to deal with a serious outbreak of CDI. The inconsistency with which outbreaks are reported (discussed in section 3.4) raises concerns that outbreaks, and more generally hyperendemic situations, are not being properly investigated and managed. It should also be remembered that survey responses were probably biased in favour of adherence to guidelines on prevention and control, since these relied on DIPCs' own assessment of their trust's performance, and some DIPCs may have relied on others for information about what measures were being implemented.

#### 5.3.2 Adequacy of current guidelines on prevention and control of CDI

There are, potentially, two reasons why existing recommendations on CDI prevention and control might need to be revisited. First, new research may question the effectiveness of existing recommendations, and / or suggest more methods of prevention and control; second, recommendations may not be adequately tailored to changing public health needs, for example they may not be sufficiently prescriptive in their requirements to implement verified prevention and control practices.

We are not aware of any research questioning the effectiveness of published recommendations for preventing and controlling *C. difficile* infection<sup>13;20;35</sup>. There are only limited recent studies suggesting alternative methods for preventing and controlling CDI. Some recent evidence has suggested that use of proton pump inhibitors is associated with higher rates of CDI<sup>36;37</sup>; it is hypothesised that decreasing production of stomach acid may lead to a reduction in antibacterial activity<sup>21</sup>. However, other papers have found no evidence of an association, and the evidence is probably still too weak for a recommendation. Studies from North America have

emphasised the role of certain quinolone antibiotics in outbreaks of CDI, and there is increasing anecdotal evidence that stopping specific antibiotics thought to be particularly responsible for new infections in an area experiencing an epidemic of *C. difficile* cases may lead to rapid control of the outbreak<sup>27;38</sup>. Although not a new finding, this research perhaps indicates that there is a case for strengthening recommendations on restricting use of particular antimicrobials as part of CDI outbreak management.

As discussed in section 2.4, the evidence for changes in the incidence, distribution and severity of CDI is suggestive but not confirmatory, and further research is needed. Should this show, for instance, that particular strains show greater transmissibility and clinical severity, more stringent guidelines on implementing of prevention and control efforts may be necessary where these strains are responsible for disease.

#### 5.4 Recommendations

*Existing recommendations for the prevention and control of CDI should be reviewed, to ensure that these adequately:*

- *promote adherence to recommendations on good antimicrobial practice, isolation of patients, and environmental cleaning and hygiene;*
- *specify procedures for reporting and managing outbreaks of CDI, including in areas with hyperendemic disease; these should also clarify when a serious untoward incident should be declared to the Strategic Health Authority or Monitor;*
- *reflect research conducted since the 1994 guidance on *C. difficile* prevention and control.*

## 6. References

1. HPA and Healthcare Commission. Interim findings from a national survey of NHS acute trusts in England, December 2005: A joint report by the Healthcare Commission and the Health Protection Agency.  
[http://www.hpa.org.uk/infections/topics\\_az/clostridium\\_difficile/menu.htm](http://www.hpa.org.uk/infections/topics_az/clostridium_difficile/menu.htm)
2. Carvel, J. 45,000 patients infected with hospital superbug. *The Guardian* . 27-8-2005.
3. Lawrence, J. Deaths from 'dirty hospital bug' double in five years. *The Independent* . 26-5-2006.
4. Bartlett JG, Perl TM. The new *Clostridium difficile*--what does it mean? *N Engl J Med* 2005;**353**:2503-5.
5. Loo VG, Libman MD, Miller MA, Bourgault AM, Frenette CH, Kelly M *et al*. *Clostridium difficile*: a formidable foe. *CMAJ* 2004;**171**:47-8.
6. McDonald LC. *Clostridium difficile*: responding to a new threat from an old enemy. *Infect Control Hosp Epidemiol* 2005;**26**:672-5.
7. Noren T. Outbreak from a high-toxin intruder: *Clostridium difficile*. *Lancet* 2005;**366**:1053-4.
8. Borriello SP. Pathogenesis of *Clostridium difficile* infection. *J Antimicrob Chemother* 1998;**41 Suppl C**:13-9.
9. Wilcox MH. *Clostridium difficile*--setting the scene. *J Antimicrob Chemother* 1998;**41 Suppl C**:1-3.
10. HPA. Voluntary reporting of *Clostridium difficile*, England, Wales, and Northern Ireland: 2004. *Commun Dis Rep CDR Wkly* 5;**15**.
11. Donaldson, L. and Beasley, C. Letter from the Chief Medical Officer and Chief Nursing Officer: Infection caused by *Clostridium difficile*. 21-12-2005. London, Department of Health.
12. HPA. Surveillance of *Clostridium difficile* associated disease: report of the National Standards Group. *Commun Dis Rep CDR Wkly* 2003;**13**:news.
13. National *Clostridium difficile* Standards Group: Report to the Department of Health. *J Hosp Infect* 2004;**56 Suppl 1**:1-38.  
[http://www.hpa.org.uk/infections/topics\\_az/clostridium\\_difficile/FINALCdiffreport.pdf](http://www.hpa.org.uk/infections/topics_az/clostridium_difficile/FINALCdiffreport.pdf)
14. HPA. Results of the first year of mandatory *Clostridium difficile* reporting: January to December 2004. *Commun Dis Rep CDR Wkly* 5;**15**:bacteraemia.
15. Deaths involving *Clostridium difficile*: England and Wales, 1999–2004. *Health Statistics Quarterly* 6;**30**:56-60.
16. Loo VG, Poirier L, Miller MA, Oughton M, Libman MD, Michaud S *et al*. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. *N Engl J Med* 2005;**353**:2442-9.

17. Pepin J, Valiquette L, Alary ME, Villemure P, Pelletier A, Forget K *et al.* *Clostridium difficile*-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. *CMAJ* 2004;**171**:466-72.
18. Frost F, Craun GF, Calderon RL. Increasing hospitalization and death possibly due to *Clostridium difficile* diarrheal disease. *Emerg Infect Dis* 1998;**4**:619-25.
19. McDonald LC, Owings M, Jernigan DB. *Clostridium difficile* infection in patients discharged from US short-stay hospitals, 1996-2003. *Emerg Infect Dis* 2006;**12**:409-15.
20. Department of Health and Public Health Laboratory Service Joint Working Group. *Clostridium difficile* Infection: Prevention and Management. 1994. London, Department of Health & Public Health Laboratory Service.
21. Louie TJ, Meddings J. *Clostridium difficile* infection in hospitals: risk factors and responses. *CMAJ* 2004;**171**:45-6.
22. Songer JG. The emergence of *Clostridium difficile* as a pathogen of food animals. *Anim Health Res Rev* 2004;**5**:321-6.
23. Severe *Clostridium difficile*--Associated disease in populations previously at low risk - Four States, 2005. *MMWR Weekly* 2005;**57**:1201-5.
24. HPA. *Clostridium difficile*: England, Wales and Northern Ireland, 2000 to 2002. *Commun Dis Rep CDR Wkly* 2003;**13**.  
<http://www.hpa.org.uk/cdr/archives/2003/cdr4003.pdf>
25. HPA. *Clostridium difficile*, England, Wales, and Northern Ireland: 2003. *Commun Dis Rep CDR Wkly* 2005;**15**.  
<http://www.hpa.org.uk/cdr/archives/2005/cdr0705.pdf>
26. HPA. *Clostridium difficile*, England, Wales, and Northern Ireland: 2004. *Commun Dis Rep CDR Wkly* 2005;**15**:bacteraemia.  
<http://www.hpa.org.uk/cdr/archives/2005/cdr2005.pdf>
27. Muto CA, Pokrywka M, Shutt K, Mendelsohn AB, Nouri K, Posey K *et al.* A large outbreak of *Clostridium difficile*-associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increased fluoroquinolone use. *Infect Control Hosp Epidemiol* 2005;**26**:273-80.
28. Brazier JS. The epidemiology and typing of *Clostridium difficile*. *J Antimicrob Chemother* 1998;**41 Suppl C**:47-57.
29. McDonald LC, Killgore GE, Thompson A, Owens RC, Jr., Kazakova SV, Sambol SP *et al.* An epidemic, toxin gene-variant strain of *Clostridium difficile*. *N Engl J Med* 2005;**353**:2433-41.
30. Pepin J, Valiquette L, Cossette B. Mortality attributable to nosocomial *Clostridium difficile*-associated disease during an epidemic caused by a hypervirulent strain in Quebec. *CMAJ* 2005;**173**:1037-42.
31. Freeman J, Fawley W, Baines S, Wilcox M. Measurement of toxin production by *Clostridium difficile*. *Lancet* 2006;**367**:982-3.

32. Hospital infection control: guidance on the control of infection in hospitals. 1995. London, Department of Health.
33. Mohan SS, McDermott BP, Parchuri S, Cunha BA. Lack of value of repeat stool testing for *Clostridium difficile* toxin. *Am J Med* 2006;**119**:356-8.
34. Delmee M, Van Broeck J, Simon A, Janssens M, Avesani V. Laboratory diagnosis of *Clostridium difficile*-associated diarrhoea: a plea for culture. *J Med Microbiol* 2005;**54**:187-91.
35. WHO. WHO Global Strategy for Containment of Antimicrobial Resistance. 2001. Switzerland, World Health Organization.
36. Cunningham R, Dale B, Undy B, Gaunt N. Proton pump inhibitors as a risk factor for *Clostridium difficile* diarrhoea. *J Hosp Infect* 2003;**54**:243-5.
37. Dial S, Delaney JA, Barkun AN, Suissa S. Use of gastric acid-suppressive agents and the risk of community-acquired *Clostridium difficile*-associated disease. *JAMA* 2005;**294**:2989-95.
38. Pepin J, Saheb N, Coulombe MA, Alary ME, Corriveau MP, Authier S *et al*. Emergence of fluoroquinolones as the predominant risk factor for *Clostridium difficile*-associated diarrhea: a cohort study during an epidemic in Quebec. *Clin Infect Dis* 2005;**41**:1254-60.

## **Appendix 1: Roles of the Health Protection Agency & Healthcare Commission**

### Role of the Health Protection Agency

The Health Protection Agency is a non-departmental public body responsible for protecting the health of people in England and Wales. One of its key roles is supporting the Department of Health's action plan to reduce levels of healthcare associated infections. The HPA provides advice to trusts and clinicians in managing and preventing cases and outbreaks of infectious disease, including those caused by *C. difficile*. It is also responsible for coordinating and analysing surveillance of infection caused by *C. difficile*, and advising the Department of Health on the suitability of such surveillance programmes.

### Role of the Healthcare Commission

The Healthcare Commission is an independent body, set up to promote and drive improvement in the quality of healthcare and public health. One of its statutory duties is to assess the performance of healthcare organisations in the NHS, and to coordinate inspections and reviews of healthcare organisations. In fulfilling this duty, the Healthcare Commission may carry out investigations into allegations of serious service failings, particularly when there are concerns for patient safety. In June 2005, the Healthcare Commission was asked to undertake an investigation into Buckinghamshire Hospitals NHS Trust, following earlier outbreaks of infection caused by *C. difficile* at Stoke Mandeville Hospital, part of Buckinghamshire Hospitals NHS Trust.

## Appendix 2: Tables of results from the *C. difficile* survey

**Table 1:** Adherence to mandatory *C. difficile* surveillance criteria for testing stool samples

	Yes ✓	No ✘	Don't know/ No answer	% of trusts testing correctly
<i>ALL diarrhoeal specimens are tested</i>	125 (83%)	21 (14%)	4 (2.7%)	83%
<i>Do NOT test non-diarrhoeal specimens</i>	116 (77%)	28 (19%)	6 (4%)	77%
<i>Community patients are tested</i>	100 (66%)	31 (24%)	19 (13%)	66%

**Table 2:** Adherence to mandatory *C. difficile* surveillance criteria for reporting stool samples

	Yes, included ✓	No, not included ✘	Don't know/ No answer	% of trusts reporting correctly
<i>Patient under care of mental health trust</i>	116 (77%)	20 (13%)	14 (10%)	77%
<i>Patient in community (PCT) hospital</i>	116 (77%)	19 (13%)	15 (10%)	77%
<i>Private patients within your trust</i>	128 (85%)	9 (6%)	13 (9%)	85%
<i>Patients in nursing/residential home</i>	117 (78%)	23 (15%)	10 (7%)	78%
<i>Patient under the care of GP</i>	120 (80%)	21 (14%)	9 (6%)	80%
<i>Patient transferred from another trust</i>	124 (82%)	13 (9%)	13 (9%)	83%
<i>In-patients admitted from nursing home with positive CD on arrival</i>	118 (78%)	19 (13%)	13 (9%)	79%
<i>Inpatients transferred from other hospitals with positive CD on arrival</i>	114 (76%)	25 (17%)	11 (7%)	76%
<i>Inpatients who have been admitted less than 48 hours</i>	136 (91%)	6 (4%)	8 (5%)	91%

**Table 3:** Reporting of cases which should not be included in reports

	No, not included	% of trusts reporting correctly
<i>Patients under 65 years</i>	128	85%
<i>Non-diarrhoeal patients</i>	112	75%
<i>Patients with positive CD result within past 28 days</i>	140	95%
<i>Toxin AND culture results on same patient</i>	112	75%
<i>Patient in independent healthcare facility</i>	33	22%

**Table 4:** Preferred denominator for mandatory surveillance of *C. difficile* (assuming separate reporting of community hospital cases possible)

Option	% preferring
Number of acute trust bed days (from HES)	19%
Number of acute trust bed days and, as a <b>separate</b> denominator, number of PCT community hospital bed days (both from HES)	43%
Number of acute trust bed days <b>combined</b> with number of PCT community hospital bed days (both from HES)	12%
ONS population estimates for people of 65 years or older	17%
Other	8%

**Table 5:** Number of trusts recording information on healthcare source on *C. difficile* samples

	Yes	No	Don't know	Total
<b>Patients from:</b>	<i>n (%)</i>			
<i>PCT community hospitals</i>	103 (77%)	25 (19%)	6 (4%)	134
<i>Mental health trust</i>	105 (77%)	26 (19%)	6 (4%)	137
<i>Independent health care facility</i>	91 (64%)	38 (27%)	6 (4%)	143
<i>Private patients in own trust</i>	89 (63%)	46 (32%)	7 (5%)	142
<i>Nursing or residential home</i>	75 (54%)	60 (43%)	4 (3%)	139
<i>GP care</i>	114 (83%)	22 (16%)	2 (1%)	138
<i>Another trust</i>	35 (25%)	101 (73%)	3 (2%)	139

**Table 6:** Number of trusts able to supply information on healthcare source of samples

	Yes	No	Don't know/ No answer	Total
<b>Patients from:</b>	<i>n (%)</i>			
<i>PCT community hospitals</i>	103 (77%)	25 (19%)	6 (4%)	134
<i>Mental health trust</i>	105 (77%)	26 (19%)	6 (4%)	137
<i>Independent health care facility</i>	91 (67%)	38 (28%)	6 (4%)	135
<i>Private patients in own trust</i>	89 (63%)	46 (32%)	7 (5%)	142
<i>Nursing or residential home</i>	75 (54%)	60 (43%)	4 (3%)	139
<i>GP care</i>	114 (83%)	22 (16%)	2 (1%)	138
<i>Another trust</i>	35 (25%)	101 (73%)	3 (2%)	139

Box 1: Mandatory surveillance - comments on usefulness of the reporting scheme

- “The problem with *C. difficile* is that it is not synonymous with disease. Yet another noose to be hung with. It has changed, together with MRSA targets, an interesting job into a miserable one”.
- “Not sure it is of any value. Specialists in microbiology & infection control know the implications of *C. diff* identification. The ways of dealing with the situation are fairly well described, both for increases in sporadic cases and in the outbreak situation so surveillance data at a national level is pretty irrelevant. Investigation of strains from outbreaks can be of significant value”.
- “No additional benefit to patients over and above the MRSA surveillance programme. I would prefer to see proper investment into modern pharmacy IT systems, so that there can be more accountability for antibiotic use by doctors, rather than hospitals named and shamed with no help given in improving the situation”.
- “Not representative of *C difficile* epidemiology in the population samples, and sampling errors are large e.g. during a norovirus outbreak more positive toxin tests are received”
- “If consistency is achieved will increase the value for benchmarking”.

**Table 7:** Types of local surveillance performed in acute trusts in England

Type of local surveillance	Number (%) of trusts performing
Local database of cases	45 (30%)
Record information on association with antibiotics	10 (7%)
Record information on clinical severity	6 (4%)
Electronic alert of previous positive cases	3 (2%)
Record ward or specialty where case diagnosed	42 (28%)
Regular (daily/weekly/monthly/quarterly/yearly) review	49 (33%)
Surveillance linked to clinician review (ICN or ICD)	22 (15%)
Other	13 (9%)

**Table 8:** Additional information useful to local management of *C. difficile* cases

Type of local surveillance	Number (%) of trusts which found this information useful
Information on association with antibiotics	60 (40%)
Information on clinical severity	11 (7%)
Information on association with ward or specialty	14 (9%)
Information on hospital environment / hygiene	15 (10%)
Information on other risk factors for <i>C. difficile</i> *	18 (12%)
Review by infection control clinician (ICN or ICD)	2 (1%)
Other	25 (17%)

\* e.g. poor nutrition, nil-by-mouth status, past medical history, length of stay, proximity to other patients with *C. difficile*, MRSA status, laxative use, previous history of CDI

**Table 9:** Proportions of trusts reporting *C. difficile* outbreaks to outside organisations

	Always	Sometimes	Never	Total responding
	<i>Number of respondents (%)</i>			
<b>CCDC</b>	84 (60%)	39 (28%)	16 (12%)	139
<b>Regional HPU</b>	51 (39%)	34 (26%)	46 (35%)	131
<b>HPA, Cfl</b>	15 (12%)	32 (26%)	78 (62%)	125
<b>SHA</b>	35 (27%)	41 (32%)	52 (41%)	128
<b>Monitor*</b>	3 (7%)	6 (14%)	34 (79%)	43

\*Foundation Trusts

**Table 10:** Areas addressed by trust policies for *C. difficile* prevention and control

	Yes	No / Don't know / blank
<i>Hand washing and hygiene</i>	134 (89%)	16 (11%)
<i>Barrier nursing</i>	130 (87%)	20 (13%)
<i>Isolation of infected patients</i>	133 (89%)	17 (11%)
<i>Control admissions to wards with excess cases / outbreaks</i>	112 (75%)	38 (25%)
<i>Recommendations for good antibiotic prescribing practice</i>	119 (79%)	31 (21%)
<i>Restrictions on use of broad spectrum antibiotics</i>	95 (63%)	55 (27%)

**Table 11:** How often do you isolate cases of *C. difficile*?

<i>Routinely</i>	93 (62%)
<i>Often</i>	38 (25%)
<i>Occasionally</i>	14 (9%)
<i>Rarely</i>	4 (3%)
<i>Never</i>	0 (0%)
<b>TOTAL RESPONDING</b>	149

## Glossary of abbreviations

ARL	Anaerobic Reference Laboratory
Cfi	Centre for Infections
CDAD	<i>Clostridium difficile</i> -associated disease
CDI	<i>Clostridium difficile</i> infection
DH	Department of Health
DIPC	Director of Infection Prevention and Control
ESBL	Extended Spectrum Beta Lactamase
GP	General Practitioner
HPA	Health Protection Agency
HES	Hospital Episode Statistics
MRSA	Meticillin-resistant <i>Staphylococcus aureus</i>
NHS	National Health Service
ONS	Office for National Statistics
PCT	Primary Care Trust
PHLS	Public Health Laboratory Service
PCR	Polymerase chain reaction