Policy development for Clostridium difficile

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The Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI) was created at the height of the incidence of Clostridium difficile infection (CDI). This article describes the role of ARHAI in the evaluation of laboratory testing for CDI, a related consultation on the legal requirements for manufacturers of in vitro diagnostic medical devices, a CDI healthcare bundle and surveillance of CDI in children.

Keywords: laboratory testing, diagnostic medical devices, surveillance, healthcare bundle

Introduction

The Advisory Committee on Antimicrobial Resistance and Healthcare-Associated Infection (ARHAI) has contributed, in particular, to four areas of guidance and policy development regarding Clostridium difficile infection (CDI): (i) evaluation of laboratory testing for CDI; (ii) legal requirements for manufacturers of in vitro diagnostic medical devices; (iii) a CDI healthcare bundle; and (iv) surveillance of CDI in children.

ARHAI came into existence in 2007, which was the peak year for reports of C. difficile infection in England as recorded by the mandatory surveillance scheme (55498 cases in the financial year 2007–08). This was also the year that enhanced surveillance for C. difficile was introduced in England. All acute NHS Trusts in England were henceforth required to report all cases of CDI in patients aged 2 years and over. Mandatory reductions for CDIs were set for Trusts, and Department of Health improvement teams intervened in Trusts that were not meeting their healthcare-associated infection trajectories. The C. difficile Ribotyping Network (CDRN) Service for England (and subsequently N. Ireland), an HPA-funded service to Trusts in England, was also introduced in 2007. These interventions were associated with the start of a 61% reduction in reports of C. difficile in England (36095, 25604 and 21698 reports in 2008–09, 2009–10 and 2010–11, respectively). The reduction was consistent with the control of the epidemic of C. difficile ribotype 027; this ribotype accounted for 55%, 36% and 22% of samples submitted to CDRN in 2007–08, 2008–09 and 2009–10, respectively. C. difficile ribotype 027 is associated with a 2–3-fold increase in mortality, and it is therefore noteworthy that the number of death certificates mentioning C. difficile, which had increased each year in England and Wales from 2238 in 2004 to 8324 in 2007, decreased for the first time in 2008 (by 29% to 5931) as the proportion of CDI cases caused by this ribotype decreased. For deaths with a mention of C. difficile, the proportion where this was the underlying cause was similar (approximately 55%) in each year until 2007, when it decreased to 49%; this proportion decreased further to 42–44% in 2008–09. The reduction in CDI reports represents a significant success story for the NHS, although untangling which interventions have proved most effective is not possible.

Evaluation of laboratory testing for CDI

Enzyme immunoassays (EIAs) for C. difficile toxins A and B have dominated the laboratory diagnosis of CDI for more than a decade. A Centre for Evidence-based Purchasing (CEP) evaluation report on C. difficile toxin assays published in 2009 found that commercial toxin assays performed poorly, with some significantly inferior to others. At best, the commercial toxin detection assays missed about 1 in 5 to 1 in 10 cases of CDI, and falsely identified 1–2 out of every 10 cases as positive. Given the poor false positive predictive values of toxin detection kits, especially in the context of widespread testing, and the possibility of missing true positives, the report and subsequent guidance advised against using these as single tests for laboratory diagnosis of CDI. After reviewing the findings of the 2009 CEP evaluation report, ARHAI recommended the need for immediate research to clarify the use of combination testing for the laboratory diagnosis of CDI. This need was emphasized by the results of the new UK National External Quality Assessment Service (NEQAS) C. difficile scheme, which was introduced in 2009. NEQAS results showed in general that testing performance was sub-optimal and that laboratories were continuing to rely on EIAs, including some that were using tests which had been found in the CEP evaluation to be inferior. The results of a Freedom of Information survey confirmed that the practice was sub-optimal. With the strong support of ARHAI, the Department of Health and HPA funded a multicentre study in England to determine the optimal algorithm for the laboratory diagnosis of CDI; the study will be the largest of its kind, with a projected
recruitment of approximately 12,500 patient faecal samples, and ended in 2011. The results of the study have been reviewed by ARHAI and used to produce new guidance on *Clostridium difficile* testing for the NHS. Such guidance is needed to optimize the laboratory diagnosis of CDI and to ensure the accuracy of surveillance data, especially given the continuing focus on reducing levels of this prominent healthcare-associated infection.\(^{10,11}\)

**Legal requirements for manufacturers of in vitro diagnostic medical devices**

Current European legislation, Directive 98/79/EC on in vitro diagnostic medical devices (IVDs), requires all manufacturers to submit a technical report as part of the Conformité Européenne (CE) marking process.\(^{12}\) This covers devices used for *in vitro* examination of specimens derived from the human body, reagents, instruments and specimen receptacles. The CE marking is an assurance of manufacturing quality and safety, but does not require that IVDs are subjected to independent performance evaluation and validation. Given the shortcomings identified in the CEP report on *C. difficile* toxin detection kits, representatives from ARHAI met with the UK Medicines and Healthcare products Regulatory Agency (MHRA) to convey concerns over the implications of using some *C. difficile* IVDs. The MHRA can formally investigate claims that IVDs are not performing to levels claimed by manufacturers, but is unable to prevent the marketing of products with limited sensitivity or specificity. The irony here is that diagnostic laboratories rely on the information provided by manufacturers about test accuracy (and are assured at least partially by the CE marking of such tests), and rarely are in a position themselves to validate assay performance. Hence, sub-optimal performance may go unrecognized and unreported. Following representations by ARHAI, the MHRA agreed to try to raise awareness about the importance of laboratories reporting concerns over the accuracy of IVDs.

It is clear that current sub-optimal approaches to CDI diagnosis raise questions about the evaluation and approval process for IVDs, particularly on the clinical utility of tests. Current European Commission legislation was adopted in 1998, and the Commission has acknowledged that it is necessary to introduce clearer definitions and requirements for safety and performance. In 2010 the European Commission (EC) carried out a consultation on technical aspects related to the revision of Directive 98/79/EC on IVD medical devices. ARHAI made submissions as part of this consultation, including formally raising its concerns over the performance of IVDs. A draft revised directive on IVDs is expected in 2012, and it is hoped that there will be greater requirement in the revised legislation for manufacturers to address the clinical utility of IVDs. If this does occur, then EC legislation on IVDs would move closer to the requirements set out in the US Food and Drug Administration legislation.\(^{13}\)

**A CDI healthcare bundle**

ARHAI is frequently asked to review draft guidelines and consultation documents. Two such examples that are relevant here are a high impact intervention care bundle to reduce the risk from *C. difficile*, and a consultation exercise about setting *C. difficile* objectives for institutions caring for children. The *C. difficile* control bundle was developed by the Department of Health in England (and was subsequently published in 2010).\(^{14}\) and consolidated guidance is provided in the Department of Health and the HPA working group report published in 2008.\(^{15}\) The *C. difficile* control bundle is based on five main factors necessary to reduce the incidence of *C. difficile* infection: prudent antibiotic prescribing, hand hygiene, environmental decontamination, isolation/cohort nursing and use of personal protective equipment. The bundle provides a tool by which institutions can audit the completeness of control measures for *C. difficile*, and emphasizes the need to address all areas to optimize infection prevention.

**Surveillance of CDI in children**

Finally, ARHAI was asked to consider the applicability of *C. difficile* objectives (mandatory targets for NHS hospitals in England) for paediatric institutions, given the uncertainty surrounding the epidemiology of CDI in children and the potential frequent, albeit very variable, prevalence of *C. difficile* in infants, which impinges on the relevance of *C. difficile* testing in this age group. Such concerns are especially pertinent for paediatric oncology units where diarrhoea can be a frequent symptom in children receiving cancer chemotherapy. At the present time, while *C. difficile* infections among young people appear to have different factors associated with them, there is currently insufficient evidence to exempt young people’s treatment providers from the CDI objective setting. However, possible ways forward include setting objectives for paediatric institutions in a different way, e.g. by benchmarking such units, possibly according to patient age profile, to take account of differences from adult CDI. Of course, where there are small numbers of positive results, it is difficult to set meaningful CDI objectives. To do so will also require more clarity on the clinical significance of *C. difficile*-positive results in children. ARHAI will review the results of the *C. difficile* testing algorithm study (see above) to determine whether this provides sufficient information to help guidance on the significance of such testing in children. In general, it is acknowledged that the evidence base in this area needs augmenting with clinical and laboratory studies that take into account the biases that have, to date, confounded progress in this area.

**Transparency declarations**

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