Institution: St George's, University of London

Unit of Assessment: A1 Clinical Medicine

Title of case study:

Improved diagnosis of *Clostridium difficile* infection through two-stage testing

1. Summary of the impact (indicative maximum 100 words)

Clostridium difficile infection (CDI) is a frequent and often fatal hospital-acquired infection. In the past, the diagnosis of CDI has been inadequate. This has had serious consequences for the management and control of infection in healthcare settings. Planche and colleagues at St George's have developed and validated a new diagnostic algorithm for CDI. This has led to policy changes in the UK Department of Health, and amongst European and US authorities, and to practical changes in the way CDI is diagnosed. Its implications for the successful understanding and management of this infection have been profound.

2. Underpinning research (indicative maximum 500 words)

Clostridium difficile infection (CDI) is estimated to result in around 3,000 deaths annually in the United Kingdom and 15,000 to 20,000 deaths in the United States, with associated case fatality rates of 6-17%. CDI typically manifests as diarrhoea, and is usually healthcare associated and related to antibiotic use. Its effective management in hospitals, and an understanding of its epidemiology is entirely dependent on accurate diagnostic testing.

Research by Planche, Krishna and colleagues at St George's in 2007-2008 identified serious inadequacies in diagnostic testing during that time. They conducted a systematic review of CDI testing procedures and demonstrated that the tests then recommended had unacceptably poor positive predictive values - often below 50% - and could no longer be recommended for clinical use [1]. They subsequently suggested that it would be preferable to use a two-stage testing procedure with an initial highly sensitive rapid screening test to identify positive samples for subsequent confirmation by a reference method.

Working with colleagues in St George's NHS Trust, Planche and Krishna, further confirmed these findings over a *prospective* 9 month period, and demonstrated that a two-stage test was superior [2]. This solution resulted in a change in practice in St. George's NHS Trust, but suffered the drawback of relying on reference assays that take up to 5 days to perform. Additionally, the variety of diagnostics, and the existence of two reference methods both reflected and added to diagnostic confusion. This was demonstrated in a survey of laboratories across England [3], which revealed great variation in diagnostic methodologies for CDI. To demonstrate the effectiveness of a two-stage strategy required a large, multi-centre study. A preliminary study of 700 faecal samples by the collaborative *C. difficile* diagnostic team at St George's demonstrated the practicality of the chosen study design in 2009. Though small, it showed that improvements in diagnosis were possible by combining tests. This paved the way for a large multicentre study sponsored by St George's with funding from the Department of Health and the Health Protection Agency, and including centres in Leeds, Oxford and University College Hospital; its aim was to define CDI diagnostics and devise a diagnostic algorithm for NHS hospitals in England. The study analysed over 12,000 stool samples and demonstrated the poor performance of individual assays and the optimum combination of dual assays. It also clearly showed the importance of the cytotoxin assay component of the two-stage test in predicting mortality [4].

3. References to the research (indicative maximum of six references)

1. Planche T, Aghaizu A, Holliman R, et al. Diagnosis of Clostridium difficile infection by toxin detection kits: a systematic review. *Lancet Infectious Diseases* 2008; **8**(12): 777-84. doi: 10.1016/S1473-3099(08)70233-0

2. Arnold A, Pope C, Bray S, et al. Prospective assessment of two-stage testing for Clostridium difficile. *Journal of Hospital infection* 2010; **76**(1): 18-22. doi: 10.1016/j.jhin.2010.03.018

3. Goldenberg SD, French GL. Diagnostic testing for Clostridium difficile: a comprehensive survey of laboratories in England. *Journal of Hospital infection* 2011; **79**(1): 4-7. doi: 10.1016/j.jhin.2010.03.018

4. Planche TD, Davies KA, Coen PG, et al. Differences in outcome according to C. difficile detection: a multicentre study of C. difficile infection. *Lancet Infectious Diseases* 2013: 13:936-45

4. Details of the impact (indicative maximum 750 words)

The initial 2008 study by Planche et al (reference 1 above) received widespread coverage in the scientific literature and also in the mainstream press [A]. The ensuing debate highlighted an appreciation of the inadequacies of current diagnostic technologies for CDI, and led to the 2009 Department of Health recommendation that enzyme immune assays should not be used as single-staged tests for CDI in England, Scotland [B] and elsewhere. This work was cited in the 2009 NHS Purchasing and Supply evaluation report (CEP080-54) [C]. In 2010, the European Society of Clinical Microbiology and Infectious Diseases also recommended a two-step protocol for the diagnosis of CDI (i.e. screening with one method, and confirming the results with another) [D]. Later in 2010, the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America jointly produced updated clinical practice guidelines for CDI diagnosis and management. These stated that enzyme immunoassay testing for toxins A and B is suboptimal, and suggested two-step testing algorithms as an interim recommendation in their clinical guidelines until more data became available [E].

The results of the diagnostic study led to a change in Department of Health and Public Health England policy for NHS hospitals in England [F]. This has led to changes in all NHS laboratories in England, and to changes in the mandatory reporting of CDI cases. Public Health England statistics for CDI infection rates across England have fallen substantially over recent years. In 2007/8 there were 55,534 cases recorded in England. In 2012/13 14,684 cases were recorded [G]. Although this marked improvement is the result of several factors including hospital cleanliness, staff awareness, antibiotic and other drug prescribing, it is also clear that accurate diagnosis - by allowing early intervention and isolation of infected individuals - has made a substantial impact on the trend.

In summary, the reach and impact of this research on validated reference assays and defined recommendations for the laboratory detection of CDI is clearly demonstrated by changed recommendations and clinical practice in the NHS, in Europe, and in the United States.

5. Sources to corroborate the impact (indicative maximum of 10 references)

A. BBC_News. C. diff testing 'is often wrong'. 2008. http://news.bbc.co.uk/1/hi/health/7702814.stm.

B. Health_Protection_Scotland. Questions and answers about the laboratory diagnosis of Clostridium difficile infection (CDI). 2012. http://www.documents.hps.scot.nhs.uk/hai/sshaip/guidelines/clostridium-difficile/clostridium-difficile-questions-answers-2009-03.pdf.

C. NHS centre for Evidence Based Purchasing, Evaluation report *Clostridium difficile* toxin detection assays CEP08054, February 2009

D. Crobach MJ, Dekkers OM, Wilcox MH, Kuijper EJ. European Society of Clinical Microbiology and Infectious Diseases (ESCMID): data review and recommendations for diagnosing Clostridium difficile-infection (CDI). *Clin Microbiol Infect* 2009; **15**(12): 1053-66. doi: 10.1111/j.1469-0691.2009.03098.x

E. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). *Infect Control Hosp Epidemiol* 2010; **31**(5): 431-511. doi: 10.1086/651706

F. Updated guidance on the diagnosis and reporting of Clostridium difficile. Epub. . 2013. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_132927. (accessed 14th January 2013 2013).

G. http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1195733750761