Institution: University of Surrey

Unit of Assessment: UOA 3 Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study:

A rapid blood-based diagnostic test for meningococcal disease adopted worldwide

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

Meningococcal meningitis is a life-threatening acute disease affecting 1.2 million people every year. Accurate and rapid diagnosis is essential for optimal patient response; however, bacterial culture tests are slow and undermined by the immediate administration of antibiotics, resulting in sterile cultures.

The Surrey team developed a rapid, non-culture-based diagnostic test for meningitis and septicaemia: this test is now routinely used for diagnosis of meningococcal disease worldwide, and was also instrumental in the implementation and monitoring of control measures for the disease, such as life-saving vaccination campaigns. Together these have contributed to the halving of adult mortality rates from meningitis worldwide.

2. Underpinning research (indicative maximum 500 words)

Meningitis and septicaemia are devastating diseases caused by *Neisseria meningitidis* (Nm). Around the world there are an estimated 1.2 million cases and 135,000 deaths due to meningococcal disease worldwide each year, mostly of children.

Recognition of the importance of early treatment led, in the 1990's, to new advice to physicians in the UK to inject suspected patients with antibiotics at first consultation. However, as the disease was conventionally confirmed by isolation of Nm from blood or cerebrospinal fluid (CSF) this raised an important issue; as antibiotic treatment led to sterile blood cultures by the time the patients reached hospital, the disease could no longer be confirmed reliably by blood or CSF culture. For example, between 1989 and 1995 approximately 20% of meningitis cases were not confirmed in the laboratory, leading to potential misdiagnosis, inappropriate treatment and lack of infection control. Correct diagnosis is essential to ensure that optimal treatment is initiated early, and there was thus an urgent need for the development of novel diagnostic tools.

The Surrey research team led by McFadden (Professor of Molecular Genetics) addressed this problem by developing a novel polymerase chain reaction (PCR)-based test. This test targeted an Nm-specific genetic element previously identified by the research team, and produced a PCR-based test with sensitivity and specificity greater than 90% for diagnosis of Nm disease from patient CSF samples (**1**). However, CSF samples can only be obtained from lumbar puncture, which is a difficult and sometimes dangerous procedure, particularly in meningitis patients. Through funding from the National Meningitis Trust and the Wellcome Trust, the research team of McFadden therefore developed a new PCR test that involved a novel purification scheme for extraction of meningococcal DNA from blood.

A double-blind clinical study of diagnosis of meningococcal meningitis in whole blood using clinical samples obtained from controls and patients demonstrated a high sensitivity and specificity on samples from patients with both septicaemia and meningitis (**1**). Importantly, the test was also shown to work on patients who had received antibiotic treatment and in whom blood cultures were negative. The test was therefore able to accurately confirm the diagnosis of meningitis in antibiotic-treated patients that were negative in the conventional culture diagnostic test. The new

blood-based PCR test thereby allowed rapid accurate diagnosis in nearly all cases of meningococcal disease.

The blood PCR test has been extensively developed and modified since its initial introduction. For example, sub-typing of the meningococcus is vitally important for epidemiological surveillance of disease and was traditionally performed by culture followed by serological typing. The frequent negativity of blood cultures prevented the use of the conventional culture-based typing method, potentially undermining epidemiological surveillance of disease. To overcome these problems in 1997 the McFadden team developed a PCR-SSCP test for non-culture-based sub-typing of the meningococcus in clinical specimens (**2**).

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

1. Newcombe J, Palmer WH, Cartwright K, and McFadden JJ. *PCR of peripheral blood for diagnosis of meningococcal disease*. Journal of Clinical Microbiology. (1996) **34 (7):** 1637-1640.
2. Newcombe J, Dyer S, Blackman L, Cartwright K, Palmer WH, and McFadden JJ. *PCR-single stranded conformational polymorphism analysis for non-culture-based subtyping of meningoccal strains in clinical specimens.* Journal of Clinical Microbiology (1997) **35(7):** 1809-1812.

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

The PCR test developed at Surrey has been established as a standard tool for meningococcal disease diagnosis in laboratories in the UK (**Ref 1**), Europe (**Ref 2**) and most developed countries (**Ref 3**). Furthermore the test is supported by the World Health Organisation (**Ref 4**) and consequently has impacted upon health and wellbeing on a global scale, with a recent study of the PCR based-assay during an epidemic of meningococcal disease in India demonstrating that it was more reliable than conventional culture in this setting (**Ref 5**). In addition to the impact of this test within the UK, the PCR-based test is rapidly becoming established as the standard across the world for both diagnosis and surveillance.

The Meningococcal Reference Unit, a specialist unit of the Health Protection Agency, performs approximately 16,000 PCR-based tests for meningococcal disease to diagnose approximately 1000 patients with the disease each year (**Ref 6**). Importantly, the PCR-based test is increasingly being used alone for the rapid, robust diagnosis of septicaemia and meningitis, with 53% of invasive meningococcal disease confirmed by PCR alone in 2010 (16,607 samples, representing 11,418 patients investigated by PCR; **Ref 7**). This increased efficiency of laboratory diagnosis can be further illustrated by the percentage of meningococcal disease cases that were laboratory confirmed, which have risen from 60% to 74% in the period 1999 – 2010, due to the effectiveness of PCR for laboratory diagnosis.

Importantly, since the adoption of the PCR-based diagnostic test, the mortality rate from meningitis and meningococcal disease has shown a steady decline in both adults and children; for example, the adult mortality rate has halved from 20 cases of mortality per million adults in 1999 to 10 cases of mortality per million adults in 2005 (**Ref 8**). This is clearly due in part to better monitoring, improved diagnosis and rapid treatment of patients facilitated by the PCR-based diagnostic test.

As well as providing a rapid and accurate test for diagnosis of meningococcal disease, the Surrey research has also stimulated the development of blood/PCR-based diagnostic tests for other pathogens. For instance, in 2008, Lehman *et al*. developed a multiplex PCR that could detect and differentiate twenty-five bacterial and fungal pathogens in blood samples (**Ref 9**). This study cites

the original 1996 Newcombe *et al*., publication as the starting point for their development.

In summary, the work of McFadden's research team pioneered a PCR-based diagnostic tool for the detection of the meningitis pathogen in patients. Adoption of this work has led to a significant worldwide Health and Wellbeing impact, both in terms of individual patient diagnosis and epidemiological surveillance. Together, these have helped reduce the mortality rate associated with meningitis and meningococcal disease, as well as allowing the successful monitoring of novel therapeutics, such as the meningitis C vaccine. Finally, the impact of this work reaches beyond meningitis alone, as it has formed the underpinning research for the development of PCR-based assays against other pathogens.

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

Ref 1. Health Protection Agency - Guidance for public health management of meningococcal disease in the UK
http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947389261

Ref 2. EFNS guideline on the management of community-acquired bacterial meningitis Chaudhuri et al., *EFNS guideline on the management of community-acquired bacterial meningitis*: report of an EFNS Task Force on acute bacterial meningitis in older children and adults. European Journal of Neurology. (2008) 15: 649-659DOI: 10.1111/j.1468-1331.2008.02193.x

Ref 3. US Centre for Disease Control and Prevention – Meningitis detection manual (2011)
http://www.cdc.gov/meningitis/lab-manual/chpt10-pcr.pdf

Ref 4. World Health Organisation – Meningitis Factsheet (2012)
http://www.who.int/mediacentre/factsheets/fs141/en/

Ref 5. Nair et al. Outbreak of meningococcal disease in and around New Delhi, India, 2005-2006: a report from a tertiary care hospital. *Epidemiology and Infection.* (2009) **137:** 570-576. DOI: 10.1017/S0950268808001398

Ref 6. Meningococcal Reference Unit – User Manual (2012)
http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947367872

Ref 7. Health Protection Agency – Meningitis detection rates (1998/1999-2011/2012)
http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/MeningococcalDisease/EpidemiologicalData/

Ref 8. Meningitis UK – UK Mortality Rates (1999-2005)
http://www.meningitisnow.org/meningitis-info/

Ref 9. Lehmann et al. A multiplex real-time PCR assay for rapid detection and differentiation of 25 bacterial and fungal pathogens from whole blood samples. *Medical Microbiology and Immunology.* (2008) **197:** 313-324 DOI: 10.1007/s00430-007-0063-0